

The Neuroanatomical Bases of Pedophilia and the Importance of Distinguishing Genuine vs. Acquired Types: A Systematic Review

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Abstract

Neurological cases of child sexual abuse (acquired pedophilia) are sometimes used as evidence for the neuroanatomical bases of pedophilia. However, these cases seem to represent a more general syndrome of impulsivity or hypersexuality than a true modification of sexual interests. Therefore, acquired pedophilia may not be adequate to investigate the neurological correlates of pedophilia. The main goal of this study was to systematically review cases of acquired pedophilia to explore the possibility that they are more closely associated with generalized behavioral impulsivity or hyperactivity than a late onset sexual interest toward children. Following the Preferred Reporting Items for Systematic reviews (PRISMA) guidelines, 64 cases of acquired pedophilia were identified. All but one were men. As expected, the mean age of onset for acquired pedophilic behaviors was higher than 50-year-old ($M = 52.8\text{-y.-o.}$, $SD = 15.6$), most cases committed various additional sexual and nonsexual impulsive acts, and only a minority (19%) showed premorbid pedophilic interests. Brain damage mostly involved basal fronto-temporal regions associated with sexual, but also impulsive behaviors. It is concluded that acquired pedophilia should not be used as evidence for the neurological bases of genuine pedophilia. Psychiatric diagnoses of pedophilic disorder would also benefit from adding an exclusion criterion based on neurological etiology. Future



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investigations are required to determine why acquired pedophilia is almost exclusively observed in men.

Keywords

acquired pedophilia, brain damage, child sexual abuse, impulsivity

“To locate the damage which destroys speech and to locate speech are two different things.”

Hughlings Jackson, 1874

“The frontal lobes exert an inhibiting or constraining influence on what Pavlov called ‘the blind force of the subcortex’—the urges and passions that might overwhelm us if left unchecked.”

Oliver Sacks, 2019

Given their theoretical and clinical implications, neurological correlates of pedophilia are intensively investigated (Jordan et al., 2020; Joyal et al., 2019; Mohnke et al., 2014). A traditional approach to study the neurological bases of behavior is to observe the overt consequences of focal brain damage. Brain-behavior associations based on classical neurological cases allowed important discoveries in the field of neuropsychology, such as the link between the ventro-orbital frontal cortex and behavioral inhibition (the case of Phineas Gage; Harlow, 1848), the contribution of lateral frontal cortical regions to speech (the case of Mr. Leborgne or Tan; Broca, 1861), and the role of bilateral hippocampi in anterograde memory (the case of Henry Molaison or HM; Scoville & Milner, 1957). Although such cases were initially used to localize cognitive functions within the vicinity of the damaged area (e.g., situating articulate language in the third circumvolution of the left frontal lobe; Broca, 1861), these simplistic brain-behavior associations were gradually abandoned with the realization that cognitive functions depend on the integrity of complex cortico-subcortical neural networks. Intriguingly, however, neurological cases of pedophilia are sometimes used to infer the neurological bases of genuine pedophilia (e.g., Alnemari et al., 2016; Perrotta, 2020; Poepl et al., 2015). As underlined by Scarpazza and colleagues (2021), that outdated approach is commonly used to investigate the neural bases of pedophilia, i.e., the study of patients who developed pedophilic urges and/or behaviors following a brain injury (the so-called acquired pedophilia or sexual behaviors toward children emerging as a consequence of a neurological disorder; Camperio Ciani et al., 2019). The temporal conjunction between brain damage or dysfunction and the emergence of pedophilic behaviors might be interpreted as evidence that the affected brain region is causally related with sexual interests in children. For instance, Mendez and Shapira (2011) suggested that “clarification of the mechanisms and pathophysiology of pedophilic behavior among patients with brain disease could shed light on the nature of [genuine] pedophilia and help develop effective, targeted interventions for this egregious behavior” (p. 1092). Similarly, Miller and colleagues (1986) argued that “[Neurological cases] offer meaningful insights into the anatomy and physiology underlying normal

sexual behaviour and provide important evidence regarding the neurological basis of aberrant sexual behaviour” (p. 867). More recently, [Lopes and colleagues \(2020\)](#) stated that “a better knowledge of the injured brain regions that have been related to the emergence of pedophilia may inform upcoming research on the neurobiology of developmental pedophilia” (p. 103).

Some years ago, we argued that most cases of neurologically acquired paraphilia represent signs of a more generalized syndrome of impulsivity or hypersexuality, not true modifications of sexual interests ([Joyal et al., 2007](#)). Concerning acquired pedophilia more specifically, [Mohnke et al. \(2014\)](#) also concluded that “in none of the above cited cases, brain pathology specifically led to paedophilia. Rather, in the majority of cases child sexual abuse occurred in the context of hypersexuality, broader changes in personality, impulse control problems and/or neuropsychological deficits” (p. 8). The main goal of the present study was to thoroughly review and update neurological cases of pedophilia to determine to what extent they truly represent acquired pedophilia or, more simply, a sign of acquired impulsivity.

Cases of acquired pedophilia also lead to suggestions that identifying cerebral (damaged) regions associated with pedophilic behaviors should help developing chemical or surgical intervention ([Lopes et al., 2020](#); [Mendez & Shapira, 2011](#)), which might (perhaps wrongfully) be applied to genuine pedophilia (e.g., [Prado et al., 2021](#); [De Ridder et al., 2009](#); for extreme examples, see [Hitchcock et al., 1972](#); [Roeder, 1966](#); [Schmidt & Schorsch, 1981](#)). Given the importance of establishing the neurological bases of pedophilia (both for theoretical and clinical reasons) and their psychiatric (diagnostic criteria) and legal (criminal responsibility) implications, this study will critically review the available literature concerning acquired pedophilia.

Brain Damage, Deviant Sexual Behaviors, and Impulsivity

Acquired and genuine (or developmental) pedophilia might be confounded, especially for professionals not working in forensic psychiatry (e.g., psychologists, physicians, lawyers). For instance, [Baird \(2020\)](#) suggested that “there are cases in which there is a clear association between a neurological condition and paedophilia or a paedophilic disorder. Such cases offer critical evidence for the role of specific brain regions in the sexual neural network” (p. 107). That statement may lead the reader to believe that neurological cases of pedophilia could be used to infer the neurobiological bases of pedophilia. However, Baird also stated (correctly) that “those who do develop paedophilia in the context of a neurological condition typically show general behavioural ‘disinhibition’” (p. 113). Indeed, a growing number of authors consider acquired pedophilia as a symptom of a larger disinhibition syndrome ([Kruger & Kneer, 2021](#); [Scarpazza et al., 2021](#)). For instance, after reviewing 19 cases of acquired pedophilia, [Scarpazza and colleagues \(2021\)](#) reported that they all suffered from a more general impulse control syndrome. Therefore, the study of acquired pedophilia might contribute minimally to our understanding of the

neurobiological bases of genuine pedophilia. From a clinical perspective, persons with acquired pedophilia seem to present a more generalized behavioral disinhibition pattern or a more generalized diminution of sexual target selectivity (hypersexuality). From a legal perspective, these neurological cases seem to have lost their volitional control while keeping the ability to distinguish wrong vs. good behaviors and their consequences (Gilbert & Focquaert, 2015). These impressions should be further confirmed, however.

The Psychiatric Diagnosis of Pedophilic Disorder

To blur a little more the picture, the mere presence of a repetitive behavior (child sexual abuse), without evidence of sexual preference or interest for children (e.g., corresponding sexual fantasies) is sufficient to receive a diagnosis of pedophilic disorder. Currently, the pedophilic disorder diagnosis is based on two main criteria: A) the presence of recurrent, intense sexual arousing fantasies, sexual urges, *or behaviors* [emphasis added] involving a prepubescent child or children (generally age 13 or less) during a period of six months or more (American Psychiatric Association [APA], 2013) or a sustained, focused, and intense pattern of sexual arousal manifested by persistent sexual thoughts, fantasies, urges, *or behaviors* [emphasis added] involving prepubertal children (World Health Organization [WHO], 2022), and; B) having committed the corresponding *behavior* [emphasis added], being distressed by the arousal (APA, 2013; WHO, 2022), or having interpersonal difficulties because of it (APA, 2013). Given that important criteria such as intensity, sustainment, and focus are not defined or operationalized in these official definitions of pedophilia, the sole presence of child sexual abuse behaviors is sufficient to give a diagnosis of pedophilic disorder in persons with neurological damage, with important implications in forensic context (Gilbert & Focquaert, 2015).

Moreover, contrarily to most diagnoses of the DSM-5 (e.g., depressive disorders, anxiety disorders, obsessive-compulsive disorders, or psychotic disorders), the pedophilic disorder does not include a differential subcategory (“due to another medical condition”) or an exclusion criterion (“the symptoms are not attributable to the physiological effects of a substance or to another medical or neurological condition”) to distinguish neurological etiology. The diagnosis of Intermittent Explosive Disorder, for instance, has the exclusion criterion of neurological origin (e.g., head trauma or Alzheimer’s disease; APA, 2013). For unspecified reasons, this is not the case for paraphilic disorders, including pedophilia.

Although an important distinction is made between child sexual abuse (the behavior) and pedophilia (fantasies, early onset, sexual preference for children) in forensic psychology, sexology and criminology (Seto, 2019), this nuance is commonly overlooked in neurology (Münch et al., 2020). However, a growing number of authors stress the difference between genuine (paraphilic preference, not only behaviors, which usually emerge during adolescence or young adulthood) and acquired pedophilia (e.g., Camperio Ciani et al., 2019; Scarpazza et al., 2021). As expected, classic signs of neurological

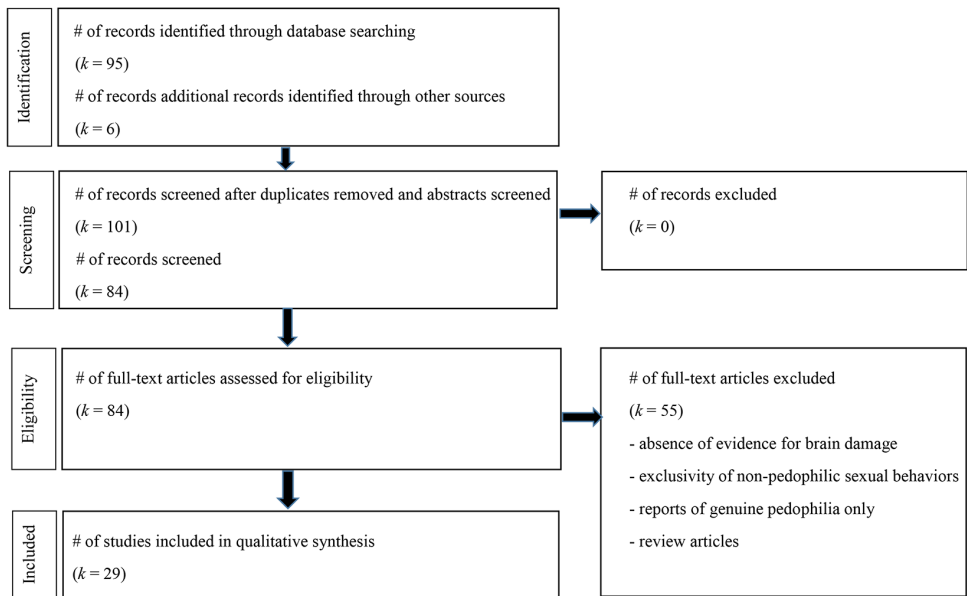
disorders distinguish men with genuine pedophilia from those with acquired pedophilia (e.g., no criminal premeditation, no history of sexual crimes, being older than 50-y.-o., no attempt to conceal, giving spontaneous confession; [Camperio Ciani et al., 2019](#)). In addition, acquired pedophilia has a clear neurological etiology, by definition (contrarily to genuine pedophilia, with unknown neurological bases), and most patients have no history of premorbid pedophilic interest (with few exceptions; [Prado et al., 2021](#); [Mendez et al., 2000](#); [Simpson et al., 1999](#)).

It is sometimes suggested that persons with acquired pedophilia already had premorbid sexual interests in children, which were released by the brain damage (disinhibiting a predisposition; [Prado et al., 2021](#); [Mendez & Shapira, 2011](#)). These cases would explain why the vast majority of patients with neurological disorders do not abuse children and why the vast majority of persons with acquired pedophilia are men (just like genuine pedophilia). However, these cases seem to be rare, although their prevalence is not clear in the literature. Another goal of this review was to estimate the proportion of persons with acquired pedophilia who had pedophilic interests prior to the brain damage.

Method

Following PRISMA guidelines ([Liberati et al., 2009](#)), a systematic literature search was conducted using Pubmed, PsychInfo, Scopus, ProQuest Dissertations and theses, and Google Scholar databases until June 2021 with the keywords “acquired” or “neuro*” or “brain injury” or “brain damage” and “pedophil*” or “child sex* abuse”. All references included in each article, all references citing each article, and all related papers were consulted. Reports published in English, French and German were reviewed. Exclusion criteria were an absence of evidence for brain damage in the case reported (e.g., cardiovascular conditions without neuroimaging), exclusivity of nonpedophilic sexual behaviors (e.g., fetishism, transvestism), studies based on genuine (developmental) pedophilia only, review papers (no inclusion of original data), and duplicated references (the same study reported in different forms; [Figure 1](#)).

Figure 1
Flow Chart of Article Search Following PRISMA Guidelines



Results

A total of 64 cases of acquired pedophilia reported in 29 publications were identified (see Table 1). Only one case was a woman (Ortego et al., 1993). As expected, the mean age of onset for pedophilic behaviors was relatively elevated ($M = 52.8$ -y.-o., $SD = 15.6$) and most cases committed various other sexual and nonsexual impulsive acts. When premorbid sexual interest ($n = 26$) were documented, the majority of cases did not show pedophilic interest behaviors prior to the brain injury ($n = 21$ or 81%), with only five cases having pedophilic interests predating brain damage (premorbid sexuality was not documented in the rest of the cases).

Table 1

Case Reports of Neurological Patients With Associated (Following/Resulting) Pedophilic Behaviors

Reports	PP	N (A)	Main official diagnosis / index crime	Brain damage / neurological diagnosis	Other sexual behaviors	Non sexual impulsivity signs
Alnemari et al., 2016	NR	1MS(+22)	Sexual desire toward children and teenagers	Left basal frontal encephalomacia Left temporal encephalomacia	Not mentioned	Attention deficits Irritability Behavioral changes
Berlin & Coyle, 1981	NR	4♂(NR)	Pedophilia	Cortical atrophy (CAT scan)	Not mentioned	Not mentioned
Berger et al., 2003	Yes	1♂(57)	Repeated sexual abuse of a 10-y.o. boy	Parkinson's disease/dopamine agonist	Fetishism Molesting a 6-y.o. girl	Not mentioned
Blumer, 1970	NR	1♂(41)	Sexual interest for 15 y.o. nephew	Right temporal lobectomy	Hypersexuality Increased sexual preoccupations Obscene language	Marked irritability Uninhibited foul talk Candy craving
Burns & Swerdlow, 2003	No	1♂(40)	Pedophilia (child pornography)	Right orbitofrontal (tumor)	Sexual advances toward stepdaughter Prostitution solicitation Sexual advances toward hospital staff and patients	Not mentioned
Casanova et al., 2002	NA	1♂(31)	Sexual perversion	Hippocampal atrophy (pyramidal cells) and schizophrenic disorder (age 69)	Bestiality Sibling incest Frequent masturbation Bisexual behaviors	Compulsive stealing General impulsiveness
(idem)	NA	1♂(57)	Pedophilia	Hippocampal atrophy (pyramidal cells) and bipolar disorder (age 85)	Bestiality Exhibitionism Transvestism Repetitive indecent advances Bisexual behaviors	Bipolar disorder

Reports	PP	N (A)	Main official diagnosis / index crime	Brain damage / neurological diagnosis	Other sexual behaviors	Non sexual impulsivity signs
Devinsky et al., 2010	No	1♂(51)	Began using child pornography	Right posterior temporal resections	Hypersexuality Coprophilia Increased masturbation Compulsive pornography	Hyperphagia Irritability Distractibility
Dimitrov et al., 1999	No	1♂(50)	Rape of a child	Right frontal ventromedial lesion	Big appetite for pornography Stories about sex with minors	Socially disinhibited Unable to handle money Unable to handle jobs Shoplifting
Fairweather, 1947	NR	24♂(NR)	Offences against little girls	Encephalitis lethargica/Post-encephalitic parkinsonism	Varied Indecent exposure Sexual assault	Varied Impulsive outbursts Violent outbursts Impulsive recklessness Self-mutilation
Frohman et al, 2002	No	1♂(36)	Sexual advances to a 12-y-o. girl Sexually assaulting another minor	Multiple Sclerosis	Asking sexually explicit questions of strangers Masturbating 10-12 times daily Touching breasts of strangers Sexual assault of an adult woman	Behavioral disinhibition Began chain-smoking
Fumagalli et al., 2015	No	1♂(71)	Pedophilia	Traumatic brain injury/lesions Right ventromedial frontal lobe Left frontopolar area Olfactory trigone Right mesial temporal lobe	Exhibitionism Frotteurism Voyeurism	Mild dysexecutive syndrome Behavioral impulsivity Aggressive personality
Gilbert & Vranič, 2015	No	1♂(48)	Physical assault and sexual harassment of pubescent step-daughter	Left frontal lobe (large tumor)	NR	Occasionally mildly aggressive
Kolářský et al., 1967	NR	1♂(NR)	Pedophilia	Temporal lobe epilepsy Perinatal head trauma	NR	NR

Reports	PP	N (A)	Main official diagnosis / index crime	Brain damage / neurological diagnosis	Other sexual behaviors	Non sexual impulsivity signs
Krafft-Ebing, 1886	NA	1♂(20)	Child sexual abuse (4-y-o. girl)	Multifocal lesions Bilateral frontal lobes First and second temporal convolutions Parts of the occipital convolutions	Bestiality	Violence (killed the victim) Antisocial behaviors
Lesniak et al., 1972	No	1♂(60)	Pedophilia	Right basal frontal lobe (tumor)	Incest Exhibitionism Bestiality Coprophilia Sexual harassment	Irritability Threatening Aggressiveness
Mendez et al., 2000 (also in Mendez & Shapira, 2011)	Yes	1♂(60)	Pedophilia (stalking, accosting, and attempting to molest children)	Focal hyponetabolism in the right inferior temporal region (Frontotemporal dementia)	Exhibitionism aiming children Increased sexual activities Increased conjugal demands	Intrudes conversations Intrudes offices Hoarding Hyperphagia Compulsive behaviors Aggressiveness
(idem)	Yes	1♂(67)	Pedophilia (repeated child molestation)	Bilateral hippocampal sclerosis	Increased sexual drive Flirt with female examiners Exhibitionism	NR
Mendez & Shapira, 2011 (in addition of Mendez et al., 2000)	NR	1♂(67)	Sexual advanced toward young daughters	Frontal lobe atrophy (bilateral) Bilateral frontotemporal hyperperfusion (Frontotemporal dementia)	Hypersexual with wife Touch breast of pictured women	Disinhibited behaviors Problems at work Compulsions Lost financial judgment Hyperorality
(idem)	No	1♂(76)	Touched children sexually	Bilateral temporal lobe atrophy (Probable Alzheimer's disease)	Making sexual comments to children	Disinhibited behaviors Too familiar with strangers Socially inappropriate

Reports	PP	N (A)	Main official diagnosis / index crime	Brain damage / neurological diagnosis	Other sexual behaviors	Non sexual impulsivity signs
(idem)	NR	1♂(62)	Sexually inappropriate with young stepdaughter	Lacunes, left caudate head Lacunes, right globus pallidus Hypometabolism, right cingulate gyrus (Vascular dementia)	Spend hours masturbating Touch people inappropriately	Disinhibited behaviors Poor impulse control Attention deficits Increased appetite
(idem)	No	1♂(59)	Child pornography	Parkinson's disease/dopamine agonist (No MRI anomaly)	Constantly seeking sex Patronize massage parlors Recurrent use of prostitution	None
(idem)	NR	1♂(32)	Sexually touched a 6-y-o girl	Huntington's disease	NR	Behavioral impulsivity Aggressiveness Attention deficits
(idem)	No	1♂(59)	Inappropriately touched 5-y-o granddaughter	Right pallidotomy (Parkinson's disease/dopamine agonist)	Sexually forced his wife Compulsive demands for oral sex Use of prostitution Excessive use of pornography Sexual advances to wife's friends Masturbation viewing a picture of granddaughter Intrusive sexual thoughts	NR, although excellent attention and executive functions are demonstrated. Impulsivity seems to be limited to sexual behaviors (hypersexuality).
Miller et al., 1986	No	1♂(50)	Propositioning children in the neighborhood	Infiltrating hypothalamic glioma	Sexual advances to 7 y.o. daughter Sexual advances to daughter's friends Frequent, increasing public sexual advances towards young children Begins collecting pornography Discusses sex almost continuously Frequently embarrass his wife	Lost financial judgment Bankruptcy
Miller & Cummings, 1991	No	1♂(64)	Had sex with a 16-y-o boy	Right frontal arteriovenous malformation (including septum, basal ganglia, hypothalamus)	NR	NR

Reports	PP	N (A)	Main official diagnosis / index crime	Brain damage / neurological diagnosis	Other sexual behaviors	Non sexual impulsivity signs
Müller et al., 2003	No	1♂(28)	Pedophilia (repeated child sexual abuse)	Right prefrontal hypometabolism (motorcycle accident/head trauma)	NR	Impulsive Behavior (including pre-morbid) Violence/impulsiveness Antisocial personality Intermittent explosive disorder Aggressive outbursts
Ortego et al., 1993	No	1♀(39)	Sex with a minor female	Multiple sclerosis (basal-orbital frontal cortex, septum, thalamus, hypothalamus, temporal cortex, brainstem, cerebellum)	Offering sex to 15 y.o. boy Bestiality Voyeurism Exhibitionism	NR
Poeppel et al., 2015	Yes	1♂(45)	Obsessional use of child pornography	Bilateral frontotemporal theta dysrhythmia (Epileptiform brain activity)	NR	Psychopathic traits
Prado et al., 2021	Yes	1♂(69)	Attempts to kiss a 7-y.o girl and granddaughter	Global cerebral atrophy Dorsomedial left frontal lobe Anterior left temporal lobe Probable behavioral frontotemporal dementia	Attempts to kiss 6 and 9-y.o. granddaughters Attempted seduction, 7-y.o. boy Premorbid incest with daughter	Several antisocial behaviors
Rainero et al., 2011	No	1♂(49)	Sexual arousal and urges toward 9 y.o. daughter	Bilateral frontal lobe atrophy Frontal bilateral hypoperfusion (Frontotemporal dementia)	NR	Verbal and physical violence
Regestein & Reich, 1978	No	1♂(56)	Repeated sexual activity with 8-y.-o. nephew	Right frontal craniotomy (Tumor)	Inappropriate with a 5-y.-o. girl Sexual solicitation of a 14-y.-o. boy Hypersexuality	None (apathy) (depression)
Sartori et al., 2016	No	1♂(64)	Sexually inappropriate behavior towards a female child in a kindergarten	Orbitofrontal cortex compression Optic chiasm compression Hypothalamus compression (Clivus Chordoma)	Pedophilic urges	Impaired at Hayling test Behavioral disinhibition Obsessions-compulsions Stealing in a museum shop

Reports	PP	N (A)	Main official diagnosis / index crime	Brain damage / neurological diagnosis	Other sexual behaviors	Non sexual impulsivity signs
Scarpazza et al., 2018	No	1♂(<70)	Pedophilia (two incidents of sexual behaviors with minor boys one year apart)	Bilateral frontal lobe atrophy (Frontotemporal dementia)	Hypersexuality	Attentional deficits Behavioral impulsivity Lack of consideration for consequences Verbal violence Hyperphagia Kleptomania
(idem)	No	1♂(<60)	Sexual behavior toward a male child	Extended brain damage (right fronto-parietal meningioma)	Repeated masturbation in front of a school	Impulse dyscontrol Impaired sustained attention Impaired inhibition Impaired planning abilities
Simpson et al., 1999	No	2♂(NR)	Child molestation	NR (Traumatic brain injury)	NR	NR
Solla et al., 2006	No	1♂(62)	Sexual interest toward granddaughter	Parkinson's disease/dopamine agonist	Bestiality (family female dog)	NR

Note. Presented in alphabetical order of first authors. N = number of participants; A = age; NR = not reported; NA = not applicable (postmortem neuropathology); PP = premorbid predisposition.

Discussion

Given the theoretical, clinical and legal importance of studying the neurological substrates of pedophilia, case studies of acquired pedophilia are commonly used as neuroanatomical models. However, the results of this review suggest that acquired pedophilia is more closely related with behavioral impulsivity in general than sexual deviance in particular. These results have several implications, which will be described in more detail below.

Brain Damage: Sexual Deviance, Hypersexuality, or General Disinhibition?

Considered alone, pedophilic behaviors following a brain injury could be interpreted as the etiology of a new sexual interest in children. When the complete clinical picture is considered, however, these pedophilic behaviors are usually one of many symptoms of a general disinhibition syndrome, or at least of a hypersexuality-related disorder. As stressed by [Starkstein and Robinson \(1997\)](#) fifteen years ago, “several studies in patients with closed head injuries, brain tumors, stroke lesions, and focal epilepsy have demonstrated a significant association between disinhibition syndromes and dysfunction of orbitofrontal and basotemporal cortices” (p. 108). The results of the present review suggest that a similar phenomenon applies to most cases of acquired pedophilia.

Three main neurobiological theories currently attempt to explain pedophilic offending (not to be confounded with nonoffending pedophilia): the frontal-dysexecutive model, the temporal-limbic model, and the dual-dysfunctional theory ([Dillien et al., 2020](#)). According to the frontal-dysexecutive model, pedophilic behaviors result from frontal lobe anomalies, leading to disinhibited behaviors. According to the temporal-limbic model, damage to the temporal lobe lead to atypical sexual interests or hypersexuality, given the limbic system involvement in emotion and motivation regulation, including sexual behaviors. The dual-dysfunctional theory merges the two models, assuming a dysfunction in both the frontal and the temporal lobes. As stressed by a growing number of authors, however, these theories explain hypersexuality and disinhibition, but not pedophilic interests *per se* ([Caffo et al., 2021](#); [Jordan et al., 2020](#); [Kruger & Kneer, 2021](#)). In view of the present results, the same conclusion can be drawn about acquired pedophilia. Interestingly, a recent brain imaging meta-analysis based on 436 men with a pedophilic disorder failed to find any structural difference compared with 449 controls ([Scarpazza et al., 2021](#)). Therefore, anomalies of fronto-temporal regions appear to be more closely associated with child sexual abuse (acting out) than pedophilia ([Dillien et al., 2020](#)). Given that several cases studies reviewed here omitted to record (or report) nonsexual signs of impulsivity, these aspects should be considered in future investigations of acquired pedophilia.

We previously reviewed and updated the neurophenomenological model of sexual arousal (Stoléru et al., 1999) through a meta-analysis of neuroimaging data (Stoléru et al., 2012). This model integrates five neuro-bio-psychological components of sexual arousal: 1) cognition (i.e., attention, appraisal, imagery); 2) emotion; 3) motivation; 4) physiology (autonomic and endocrine responses), and; 5) inhibition. Although the cognitive component is the most complex, it depends crucially upon the inhibitory component (modulatory function), which therefore plays a prominent role in the frequency and target of sexual arousal. The inhibitory component includes three subcomponents: 1) latency inhibition (occurring during periods between sexual arousal and blocking its emergence); 2) devaluation (cognitive inhibition decreasing the sexual relevance of a stimulus when the context or the target is inadequate); and; 3) withholding an action (behavioral inhibition of the overt expression of sexual arousal). It is worth noting that neurological substrates of these inhibitory subcomponents are commonly affected in cases of acquired pedophilia (as described in Table 1; see also Kruger & Kneer, 2021; Mohnke et al., 2014), including the lateral orbitofrontal and temporal cortices (latency inhibition), the medial orbitofrontal cortex (devaluation), and the basal ganglia (caudate nucleus; withholding). These results are in line with the suggestion that a deficit in one or more inhibitory components of sexual arousal explains a significant part of acquired pedophilia. Although this type of pedophilia may meet the DSM-5 criteria, it is usually not associated with the essential features of a paraphilia (i.e., sexual preference and sexual fantasies). This conclusion argues for the addition of neurological damage as an exclusion criterion for the pedophilic disorder, just as it is the case for most other DSM-5 diagnoses.

As stressed more than 10 years ago by First and Halon (2008), “diagnostically, one error that can result in a false positive diagnosis (i.e., opining that a paraphilia is present in the respondent when it is not) is to base the diagnosis solely on the presence of the criminal sexual behavior without evidence causally connecting that behavior to the paraphilic arousal pattern” (p. 446). Similarly, the Working Group on the Classification of Sexual Disorders and Sexual Health of the ICD-11 rightfully stressed that a history of sexual behavior involving children *should not be sufficient* [emphasis added] to establish the diagnosis of pedophilic disorder because an essential feature of the condition is a sustained, focused and intense pattern of sexual arousal to prepubescent children (Krueger et al., 2017). Krueger et al. (2017) specifically stated that when only behaviors are present, other causes should be considered because of the possibility of nonsexual or other explanations for these behaviors (p. 1537). It could be argued that a brain injury should be considered as an exclusion criterion (i.e., other explanation) for the pedophilic disorder. However, given the lack of operationalization and instruments for assessing the criteria of sustained, focused and intense interests, many cases of pedophilia are still based solely on behaviors (especially in neurology), without the required sexual arousal pattern, preference or specificity.

It would be interesting to assess sexual fantasies of men with acquired pedophilia. Although seldom reported in existing studies, there is a possibility that acts of child sexual abuse following brain injury are not only unpremeditated, but also unassociated with corresponding sexual fantasies. The presence of these sexual urges without corresponding sexual fantasies might further help distinguishing acquired pedophilia from genuine pedophilia. Developing and providing validated measures of such important criteria for a pedophilic disorder as intensity and focus of sexual interests would also significantly contribute to the confirmation of the diagnosis in neurological cases of child sexual abuse.

Legal Implications

The study of acquired pedophilia has important legal implications because the condition is usually associated with a special neuropsychological pairing, i.e., a loss of volitional control with preserved insight, awareness and/or moral. The preservation of insight, in turn, commonly lead the justice system to consider persons with acquired pedophilia to be responsible of their acts, with all the legal consequences associated with these decisions (Gilbert & Focquaert, 2015). Although offenders with acquired pedophilia might indeed be well aware of the wrongfulness of their acts (*mens rea*, “guilty mind”), the brain damage explains in large part their acting out because it results from a significant reduction of volitional control and behavioral inhibition (*actus reus*, “guilty act”). Therefore, the difference in etiology, motivation, and context between acquired and genuine pedophilia should have important legal implications (Scarpazza et al., 2018). As underlined by Gilbert and colleagues (2016), an impaired capacity to control one’s behavior and urges due to neurological damage should mitigate criminal responsibility. It could also help choosing more appropriate treatment plans (e.g., more closely related with neurological disorders than paraphilic disorders).

Acquired Pedophilia: A Male Disorder

Although sexual interest in children is relatively rare in women, it is reported by a small minority among the general population (Wurtele et al., 2014). One notable result from this review is the quasi exclusivity of male cases. If damage to fronto-temporal neural networks simply provoke a generalized disinhibition (as suggested here), including sexual urges toward children, both men and women with similar brain damage should show acquired pedophilia. This sex imbalance is reminiscent of that observed in most cases of paraphilic disorders. It remains possible that neurobiological factors (e.g., neurohormones, genes) closely associated with sex drive and male gender (e.g., testosterone, X chromosome) play a mediating role between brain damage and sexual abuse of children leading to acquired pedophilia. It remains also possible that damage to subcortical structures associated with sexual behaviors (e.g., amygdala, hypothalamus)

distinguishes disinhibition syndromes with vs. without pedophilic manifestations. Future interdisciplinary investigations will help disentangling these etiological factors of acquired pedophilia.

Conclusion

Studies in behavioral neurology generally led to the conclusion that acquired pedophilia has three main types of origins, associated with lesions to three main cerebral regions: 1) a general disinhibition syndrome induced by basal-orbital frontal damage; 2) hypersexuality following temporal subcortical damage (e.g., hypothalamus, hippocampus) and; 3) a true modification of sexual interest, associated with temporal amygdala lesions (Mendez & Shapira, 2011). In view of the present results, it is suggested that disinhibition and hypersexuality but not true modification of sexual interest are associated with acquire pedophilia.

As recently concluded by Kruger and Kneer (2021), “for a long time, a so-called ‘symptomatic’ sexual deviance (including pedophilic behaviors) was reported after brain injury [...]. These observations may not necessarily reflect a genuine change of sexual preference or a disclosure of a latent paraphilic disorder, but may indicate the importance of intact brain function for controlling sexual behaviors, particularly temporal and frontal regions. Sexual disinhibition might explain a non-specific broadening of sexual behaviors (like a disturbance of a sexual filter system) that may include deviant ones.” (p. 72). The results of this review concord with that conclusion. It could also be suggested that damage to basal fronto-temporal regions induce a disturbance of a general filter, prompting both sexual and nonsexual impulsive acts, including pedophilic behaviors. Therefore, cases of acquired pedophilia may not be adequate (or at least optimal) to infer the neurological bases of pedophilia.

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Note. Asterisk (*) marks references included in Table 1.

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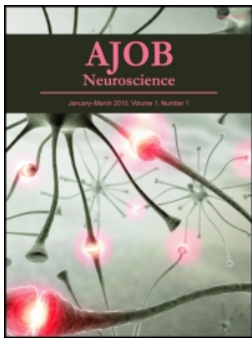


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I Miss Being Me: Phenomenological Effects of Deep Brain Stimulation

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I Miss Being Me: Phenomenological Effects of Deep Brain Stimulation

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The phenomenological effects of deep brain stimulation (DBS) on the self of the patient remains poorly understood and under described in the literature, despite growing evidence that a significant number of patients experience postoperative neuropsychiatric changes. To address this lack of phenomenological evidence, we conducted in-depth, semistructured interviews with 17 patients with Parkinson's disease who had undergone DBS. Exploring the subjective character specific to patients' experience of being implanted gives empirical and conceptual understanding of the potential phenomenon of DBS-induced self-estrangement. Our study concluded that (1) the more patients preoperatively felt alienated by their illness, the more they experienced postoperative self-estrangement, and (2) the notion of self-estrangement seems to exist in association with certain common qualitative characters, namely, loss of control, which reflects a deteriorative estrangement, and distorted perception of capacities, which reveals a restorative estrangement. These findings indicate that subjective self-reports help us to understand some aspects of the potential phenomenon of DBS-induced self-estrangement.

Keywords: alienation, deep brain stimulation, distorted perception, loss of control, Parkinson's disease, self, side effects, self-estrangement

Despite growing evidence that a significant number of patients experience postoperative neuropsychiatric changes (Volkman, Daniels, and Witt 2010; Muller and Christen 2011, Clausen 2010), including reports of irreversible alteration following removal of implants (Gilbert 2013a), the phenomenological effects of deep brain stimulation (DBS) on the patient's self remain poorly understood and underdescribed in the literature. Most postoperative reports emerging from clinical studies measure standard cognitive, psychometric, and functional scales (Smeding et al. 2011; Lewis et al. 2015; Pham et al. 2015; Schoenberg et al. 2015). Most discussion of the postoperative changes following the implantation of brain devices such as DBS focuses on abnormal side effects caused by the intervention (e.g., hypersexuality, hypomania). By contrast, relatively little attention is paid to the idea that successfully "treated" individuals might experience difficulties in

adjusting to becoming "symptom free": a phenomenon that is known as the "burden of normality" and that can lead to postoperative iatrogenic harms (Gilbert 2012; Wilson, Bladin, and Saling 2007). The risk of postoperative iatrogenic harms can be extremely serious; in a statistically significant number of clinical trials, implanted patients have attempted or died by suicide (neurological condition: Temel et al. 2009; psychiatric condition: Gilbert 2013a; Gilbert 2013b). Given the failure of studies to faithfully capture patients' experience of a "new" postoperative self, potential DBS-induced phenomenological effects on patients' self remain largely unexplored. DBS's nontarget effects and their impact on patients' self are particularly concerning, given the number of patients being implanted for approved therapy (more than 100,000) and the increasing number enrolled in experimental trials (Medtronic 2013).

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To our knowledge, only a small number of studies in the literature have specifically addressed the phenomenology of the self through a patient's subjective experience with DBS (de Haan et al. 2015; de Haan et al. 2013, Hariz et al. 2011, Schüpbach et al. 2006). A small number of case reports provide further insight into some of these postoperative changes to the self. With so few phenomenological investigations into the experience of self, the philosophical debates about potential postoperative effects of DBS on the self are mostly based on anecdotal cases that may not be representative, but are used to serve authors' arguments. It is essential to supplement the current literature with more rigorous empirical studies exploring the phenomenological effects of DBS on the self. Studying patient's first-personal experience of DBS through the unique phenomenological lens to explore patient's self-perception will shed light on current philosophical disputes, but most importantly, will guide prospective patients through decision-making processes leading to implantation.

To address this lack of phenomenological evidence, we conducted in-depth, semistructured interviews using open-ended questions with 17 patients with Parkinson's disease (PD) implanted with DBS in Australia, from the states of Victoria, Tasmania, and Queensland.¹ The average duration of the interviews was 45 minutes. This qualitative approach allowed us to capture first-personal perspectives that are not identified by standardized questionnaires and scales. Three independent researchers conducted the interviews and transcribed the content. All interviews were conducted in English. Interviews were analyzed by grouping patients' self-experience into four main phenomenological clusters of experience: (1) degrees of alienation caused by PD or benefit caused by PD; (2) postoperative feelings of enablement or powerlessness; (3) postoperative feelings of embodiment or disembodiment; and (4) reports of postoperative changes by partner/family members. These clusters were then divided by subthemes, which were populated by patients' key answers and quotes. Table 1 reports patients' details, and Appendix 1 is the semistructured questionnaire used to guide our interviews. Our aim was to explore perceptions of self-change by patients implanted with DBS. As this is a qualitative study based on first-personal narratives involving more than 765 minutes of interviews, the results are highlighted and given in excerpt format.

This article (1) reports our general findings; (2) reports and discusses findings related to deteriorative and restorative self-estrangement; (3) discusses embodiment through patients' accounts of experiencing DBS implants as being

part of them; (4) summarizes the notion of self-estrangement; (5) advocates that DBS alone does not directly causes potential self-estrangement; (6) indicates some limits of our research; and (7) provides general conclusions from our collected data.

PATIENT SUBJECTIVE ACCOUNTS: EXPERIENCING SELF-ESTRANGEMENT

Before reporting our results, we need to define some terminology. Exploring the phenomenon of DBS postoperative self-estrangement involves an examination of whether experiencing self-estrangement involves certain qualitative experiences as phenomenally characterized by implanted patients. From a phenomenological perspective, if we define the self as, broadly construed, the subject of one's phenomenological experience of X (e.g., X being an emotion, perception, thought, etc.), then we understand that the very existence of some particular phenomenological experiences can qualitatively reflect the self. By experience, as Strawson formulated it, we understand experiential "what-it's-likeness" (Strawson 2011).² The existence of a self qualitatively experiencing X is given with the existence of experiencing X. In other words, experiencing DBS likely entails specific or common qualitative experiences; we aimed to explore these specific or common DBS-related experiences, especially any experiences of estrangement. By looking at the subjective character specific to patients' experience of being implanted, especially through phenomenological experience of first-personal or subjective change, we believe we can gain better empirical and conceptual understanding of the phenomenology of potential DBS-induced self-estrangement.

Our study reveals that there is a strong correlation between postoperative estrangement and how patients preoperatively perceive themselves with respect to their illness. In other words, 100% of patients who perceived PD as not intruding on their life did not experience feelings of estrangement ($n = 4$). For instance, Patient 08 and Patient 12 clearly articulated this correlation:

Patient 08: "The disease is part of me. You can't separate from the disease" and "I don't think [DBS] changed me, it hasn't changed my personality or who I am, or how I feel about myself."

Patient 12: "[Parkinson's] is not a painful experience . . . I was able to do things and contribute to society in ways I would otherwise have been unable to do" and later pointed out that "[DBS] has not changed who I am, it's improved."

1. This study was conducted in accordance with the Tasmanian Human Research Ethics Committee regulations. Patient Consent and Minimal Risk Ethics Application Approval, entitled "H0014820 Deep Brain Stimulation and Postoperative Self-Adjustment Phenomenon," are also in compliance with the Tasmanian Human Research Ethics Committee regulations. Ethical approval was obtained in May 2015.

2. We draw on Strawson's account here in order to justify looking at the subjective experience of DBS implantation. We do recognize, however, that this is a "thin" account of the self and that Strawson's conception of phenomenology can be contrasted with a "thick" account, which takes agency and embodiment as defining of the phenomenological standpoint.

Table 1. Patients' general information.

Patient	Age (surgery)	Gender	Time span between surgery and interview	Time span between PD diagnostic and surgery
P01	64 years old	F	1 year 6 months	10 years
P02	68 years old	F	1 year	20 years
P03	68 years old	M	2 years 2 months	12 years
P04	52 years old*	F	1 year 2 months	6 years
P05	82 years old	F	3 years	12 years
P06	63 years old	M	1 year	8 years
P07	53 years old	F	4 years	9 years
P08	50 years old	M	6 years	9 years
P09	54 years old*	F	5 years	16 years
P10	58 years old	M	1 year	11 years
P11	50 years old	M	6 years	10 years
P12	66 years old	M	1 year	11 years
P13	66 years old	M	2 years	6 years
P14	40 years old	M	4 years	7 years
P15	69 years old	M	4 years	19 years
P16	**	F	3 years 6 months	**
P17	52 years old	M	5 years	8 years

*Patients had two surgeries. Patients' ages during the second surgery.

**Was not provided.

In parallel with this strong correlation between preoperative perception of oneself through disease and a sense of estrangement, we observed that patients (61%) who felt alienated by their illness were likely to experience, to various degrees and intermittently, some postoperative feelings of self-estrangement ($n = 8$). For example:

Patient 16: "[Parkinson's disease] really takes over. ... I couldn't work which was a big part of my identity. ... If I didn't have the device I'd probably be dead right now" and later states "I think that [DBS] does change you as a person."

Our findings indicate that the more patients preoperatively felt alienated by their illness, the more they experienced postoperative self-estrangement. The question that needs to be addressed in the next section is how experiencing DBS self-estrangement correlates with some specific qualitative character common to some implanted patients.³

3. In our study all patients (4 out of 4; 100%) reporting that PD enhanced their life also reported a general feeling of postoperative self-continuity. Some patients clearly experienced the opposite (8 out of 13; 61%): namely, they self-reported how PD devastated their existence, and simultaneously reported how they experienced postoperatively various degrees, intermittences, and intensities of estrangement. For the five remaining patients (5 out of 13; 38%), their reports are too unclear to be classified. They experienced PD as intruding in their life, but didn't clearly report significant postoperative estrangement. Thus, they couldn't fit in our classification of restorative or deteriorative estrangement.

EXPERIENCING DETERIORATIVE AND RESTORATIVE SELF-ESTRANGEMENT

Our study found that postoperative self-estrangement could be phenomenally experienced as deteriorative or restorative by implanted patients. Deteriorative or restorative self-estrangement involves experiencing an involuntary shift in the qualitative character. For instance:

Patient 04: "I can't be the real me anymore—I can't pretend ... I think that I felt that the person that I have been [since the intervention] was somehow observing somebody else, but it wasn't me. ... I feel like I am who I am now. But it's not the *me* that went into the surgery that time. ... My family say they grieve for the old [me] ..."

Interviewer 2: "What have your children said to you about the difference that they've seen before and after?"

Patient 04: "Yes, they said they don't recognize me."

Interviewer 2: "And in what way don't they recognize you?"

Patient 04: "That I am so impulsive and seem to change my mind all the time."

What characterizes Patient 04's postoperative feelings of estrangement, as in other cases, can be understood by way of the deteriorative effects on the patient's self. We believe Patient 04 mostly experienced deteriorative consequences because Patient 04's feelings of estrangement largely appear to be correlated with a radical and ongoing sense of loss of control over her previous self, which reflects an involuntary and unintentional shift in her qualitative character. For instance, Patient 04 reported developing postoperative ongoing mania (medically diagnosed),

leading to a suicide attempt, as well as a substantial increase in impulsivity. Patient 04 said, "I cannot control the impulse to go off if I'm angry." As such, these findings appear to further corroborate the hypothesis that deteriorative self-experiences seem to qualitatively characterize the notion of powerlessness (Gilbert 2013a, 2015a), often manifested through involuntary self-harming actions/behaviors and/or loss of control.

It is a common mistake to think that postoperative feelings of self-estrangement are qualitatively deteriorative. Our study exposes that although DBS diminishes symptoms and restores patients' control over their lives, more patients experienced feelings of restorative estrangement rather than deteriorative estrangement. For instance:

Patient 13: "[DBS] has allowed me to return almost to the person I was before ... It's allowed me to be what I am, rather than change what I am," but while discussing this sudden restorative feeling, Patient 13 confessed that DBS adversely resulted in intermittent uncontrollable emotional sensitivity, to the extent of experiencing "a state of hysterics ... I felt like I had lost my true self, it [is] way behind me."

Patient 13's experiences of restorative estrangement seem to separate an old self (practically understood), "DBS has partly restored my autonomy," and a postoperative qualitative character of this patient's selfhood, "I had lost my true self" as a result of the disease. Patient 13's comments illustrate that restorative estrangement can come in degrees. In this respect, a patient might experience self-rejuvenation while observing an involuntary shift in some aspects of her qualitative character. Similarly:

Patient 11 first claimed: "it wasn't so much that it changed who you are, it rather restored who you are," but he later confessed that this novel restorative empowerment originated an uncontrollable phenomenon from which he dissociated his self and does not recognize himself: "There's nothing that I can do [to stop this] 'emotional incontinence'⁴ as I call it. ... If I had a choice I would say, 'Look see what you can do ... to stop me from doing that.' Because it does get embarrassing."

Patient 11's postoperative feelings of restorative estrangement appear to increase some restorative capacities that the patient seems to identify with as essential for his preoperative and predisease self while admitting losing control of other aspects of his postoperative self. Aligning with these feelings of postoperative restorative estrangement:

Patient 09 stated: "I felt I was 15 years younger after the operation ... I felt so strong and confident ... I could do anything ... I felt so good I tried to move the pool table and I ruptured the disc in my back ... I blame DBS for that because I felt so good, I did something that I couldn't have done when I was

21 and I don't know why I thought I could do it when I was 54 ... I was in a wheel chair for 2 months."

Patient 09 "blames" the device for her ruptured disc (i.e., she accepts it was her fault, but she attributes her unreasonable confidence to the success of the device). We observed that sometimes the device provided such levels of heightened and uncharacteristic confidence that this resulted in other unforeseen difficulties. For example, Patient 06 observed that he was bold in his activities, had difficulties in refraining from engaging in numerous commitments, and that he was in conflict with his wife: "I think I have been causing a bit of problems in my relationships by being just so full on. ... I have to slow down that activity and make it more manageable for myself and my wife." In a similar way, Patient 09 was so confident in her newfound strength and physical capabilities that she was nearly permanently disabled when she attempted to lift and move a large pool table. In this way, DBS may be construed as so effective in relieving symptoms that it actually causes people to have a distorted view of their own capabilities. These distorted perceptions appear to induce the belief that patients have (some) enhanced capacities far in excess of their actual abilities. These distorted views of their capacities are often described in the language of sudden unexpected strength.

For instance, Patient 07 described her feelings after suddenly acting out of character during calibration. She reported starting walking and wanting to reach her husband's location (i.e., by foot), which would have taken her days. She explained her decision later by saying:

"Oh God, I wasn't me, and I knew I wasn't me and there was nothing I could do about it ... I knew what it was! I knew [DBS] had been turned up that day. Unlike the drugs which creep up on you, and you don't know what's happening. With [DBS] I knew what it was, so I knew it was fixable."

Here again, the device is similarly "blamed" for the sudden restorative strength. The device is responsible, "I knew what it was! I knew [DBS] had been turned up that day," for the distorted interpretation of her own capacities, "I knew I wasn't [my capacities]."

In parallel, while describing a sense of loss of control, Patient 04 also recognized DBS had given her increased feelings of strength (despite having mostly suffered from deteriorative estrangement):

"I never had felt this lack of power or this giving of power—until I had deep brain stimulation ... It's like the psychologist said [to me]: for a woman who had a very invasive brain surgery nine days ago and you've just walked 10 kilometres [to get to your appointment]. And on the way I stopped and bought a very uncharacteristic dress, backless—completely different to what I usually do."

Here, Patient 04's "lack of power" in some aspects of her character seems to be replaced by a "giving of power" with respect to other novel qualitative features of character—that

4. DBS has turned Patient 11 into a SNAG (patient words), a phenomenon beyond his control and putting him in discomfort. A SNAG is an acronym for "Sensitive New Age Guy."

is, a loss of control leading to a disinhibition that is characterized by some incommensurable feelings of strength.

The collected restorative narratives seem to indicate that DBS can distort patients' feelings of who they are or make them feel like they aren't themselves in some ways, capable of reaching unwanted limits beyond the preoperative self, for instance, as well as inducing unintended estrangement experiences of being in the world.

Given the preceding discussion, our study shows that the notion of self-estrangement seems to exist in association with certain common qualitative characters: namely, loss of control, which reflects a deteriorative estrangement, and distorted perception of capacities, which reveals a restorative estrangement.

EMBODIMENT: HAVING A BRAIN IMPLANT VERSUS BEING A BRAIN IMPLANT

Another way to understand how DBS might induce feelings of estrangement is to examine whether DBS has an effect in terms of being understood as a foreign intrusion; that is, whether the patients viewed the device as being a part of, or not a part of, themselves. For instance, for Patient 08, "It's just become part of me. It's more the other way around. It's more the DBS becomes a part of who you are rather than changing you." In this case the patient identifies with or sees him- or herself as continuous with his or her stimulated self. In contrast, when the device is seen as other or an outside force, it could contribute to feelings of self-estrangement.

However, our study found that the hypothesis—that if patients incorporate the DBS device into their self-image/body schema, then they will suffer less from self-estrangement—is not as robust as it sounds. In general, the patients interviewed did not notice the device in their body while it was doing its job in the background, despite having experienced some degrees and intermittent episodes of self-estrangement. Many noted that the device had a minimal presence in their body and that they did not typically notice that it was there. For example, Patient 13 declared, "I charged myself up this morning"; Patient 12 asserted, "I just don't know it's there. I don't feel invaded." Patient 06 affirmed, "It's part of me." Patient 05 indicated, "More a part of my body." Such responses appear to illustrate that patients use a language that seemingly incorporates the DBS device into their self or body image. Patient 13 clearly uses such metaphorical language; he does not say "I charged the devices up this morning" but rather "I charged myself up." Such language could indicate an embodied acceptance of the implant, of patients feeling like being one with the implant.

Nonetheless, we did find a correlative example between the device felt as an alien entity and a patient experiencing self-estrangement. Patient 04, who experienced the most severe and harmful effects of estrangement in our study, declared the following in response to the interviewer's question:

Interviewer 1: "The implant, do you feel that it is part of you?"

Patient 04: "No!"

Interviewer 1: "You feel that it is alien?"

Patient 04: "I hate it. I wish I could pull it out!"

Aside from this obvious case with Patient 04, who clearly experienced having a foreign device rather than it being part of her (i.e., language of being the device), most patients incorporated the devices. A few complained that it hampered, or had hampered, physical activity in the past. Patient 08 said, "I used to be able to feel the electricity going through my body but I don't feel it now . . . I forget about it most of the time, but I am aware because there is a hard little thing on your chest." Others had (perhaps unwarranted) fears about others interfering with the device accidentally (one research participant instructed hairdressers not to use clippers on her neck in case it damaged the wires). But in general, patients seemed to regard the device as something that had been integrated into their body. Most did not view it as a foreign entity that existed separately from their own self. The fact that patients tend to forget about the DBS implant might be construed as a positive thing because, in the end, they may focus less on their disease. This perception prevents DBS from having a felt intrusive quality. An interesting general point is that patients with non-rechargeable devices seemed not to notice the device as much, and it didn't have as much presence to them. Some patients with rechargeable devices noticed it a lot more, sometimes obsessing over its charge.⁵

In addition to exploring whether and how the implant altered patients' relationship to their body, we can explore the relationship to changed capacities of the body. Patients' measure of restoration often correlated with their physical abilities, and they declared being more independent (e.g., patients 16 and 17). However, as also noted in the preceding, some patients overestimated their capacities, in some cases beyond what they were capable of prior to the stimulation and the onset of PD. These experiences were often connected with a feeling of a loss or lack of control.

SUMMARIZING DBS POSTOPERATIVE SELF-ESTRANGEMENT

Our study demonstrates that there are various qualitatively different kinds of self-estrangement experiences. To speak of a postoperative estrangement implies that

5. There were some fears concerning what would happen if the device was not charged correctly (i.e., for those with rechargeable batteries). Some research participants took a very conservative attitude toward the battery charge and constantly monitored and topped up the battery. Others were very casual and let the battery run down a lot. The people who were concerned about monitoring the charge level were also people who seemed to have some anxieties about the implications of what would happen if the device ran out of power. Those who were more casual seemed to not harbor those sorts of fears. One person accidentally turned off his device at one point and only noticed a few hours later when he had trouble typing. But it was easily remedied and the event did not bother him or give him any further anxieties.

the relevant patient experience of deteriorative or restorative estrangement has an irreducibly subjective character specific to the implanted individual (Atkins 2000). The postoperative feelings of estrangement constitute a patient's first-personal point of view of a qualitatively deteriorative or restorative experience. Experiencing deteriorative or restorative self-estrangement does not mean a subject is experiencing X differently (e.g., X being an emotion, perception, thought, etc.), but rather that the experience of being the subject of X is qualitatively different. Experiencing X differently is not the same as experiencing oneself as qualitatively different. In other words, in some cases, the experience of X can feel different while the experiencer remains identical. Accordingly, an experiencer can feel estranged while the experience of X feels identical in some cases. In that respect, being self-estranged cannot be reduced to experiencing X differently; it rather involves an irreducibly novel experience of being the subjective character of X (experiencer is necessarily qualitatively different, but not necessarily X). Being a subject of X does not involve estrangement when the subjective experience is identical.

DBS ALONE DOES NOT DIRECTLY CAUSE POTENTIAL SELF-ESTRANGEMENT

There is a lack of consensus about how to adequately characterize the self vis-à-vis DBS treatment within the neuroethical literature. The current state of the debate is eclectic. Table 2 shows the numerous theoretical models of the self motivated to explain the effects of DBS on the self, including, but not limited to, the self as characterized by "self-representational capacities" (Synofizik and Schlaepfer 2008); as a "foundational-functional model" (Witt et al. 2013); as narrative self-constitution (Schechtman 2010) or relational narrative constitution (Baylis 2013); as an "enactive, affordance-based model" (De Haan et al. 2013); and as a "pattern theory of self" (Dings and de Bruin 2015). In addition to various models of the self, there is disagreement about the central concept affected by DBS, autonomy, and/or identity, and how to characterize these effects—for example, autonomy in terms of patient autonomy or competence, loss of control, and identity in terms of changes to personality or psychological continuity, to name a few. The conceptual understanding of agency also varies in these accounts. Most philosophical discussions concerned with potential DBS-induced effects on the self are not based on firsthand studies (see Table 2).⁶ Also, when examining the firsthand studies from which the philosophical debate is inspired, we

quickly observe that these studies describe a wide range of anatomical targets, as well as a diversity of unwanted personality changes associated with postoperative DBS intervention.

Further, there is a potential to claim that DBS directly causes these changes. It is often inferred in the nonscientific literature that DBS intervention poses a postoperative threat to personal identity, or induces some unwanted personality changes or has an unintended effect on the self. For instance, some have written, "The risk of becoming another person following surgery is alarming" (Witt et al. 2013) and "personality changes represent a threat to personal identity and agency" (Schechtman 2010). We categorize these positions as a "post hoc ergo propter hoc"-related assumption. Many neuroethical and philosophical documents⁷ are guilty of perpetuating this assumption with little examination or scrutiny.

What do subjective self-reports from PD patients with DBS show us about the potential for self-estrangement? Our study found that 8 patients among 17 (47%) experienced some degrees of, and intermittent episodes of, self-estrangement. These results align with clinical reports, which indicate that the phenomenon of "becoming a different person" after DBS intervention may not be solely attributed to the electrical stimulation itself but could be caused by treatment adjustments post surgery or by disease progression (Volkmann, Daniels, and Witt 2010). As such, the prevalence and incidence of self-estrangement might not be exclusively correlated with a specific DBS target and/or stimulation parameter but rather should be seen as a result of the interaction between the neural and glial effects of electrode insertion during surgery (Vedam-Mai et al. 2012) and electrical stimulation, adjustments in medication, and natural progression of the disease (Volkmann, Daniels, and Witt 2010), especially when DBS is used in patients with neurodegenerative disorders where changes to personality and identity are inevitable regardless of treatment course and choices. Although DBS affects spiking activity and neurotransmitter release in local (Hammond et al. 2008; Cheney et al. 2013) and distant circuits (Li et al. 2014), turning off stimulation won't conclusively allow dissociation of personal identity changes as a result of electrical stimulation from DBS and as a result of associated treatment modifications and disease prognosis. This is further complicated by the potential of DBS to induce long-term synaptic changes in the brain (Herrington, Cheng, and Eskandar 2015). However, some case reports do seem to suggest that turning off the stimulation ends, for instance, an episode of mania or impulsivity (Tsai et al. 2010), and if longer term synaptic changes are made, then we might not expect the personality changes to disappear with the removal of stimulation (Gilbert 2013b). Overall, changes in identity, personality, and self-awareness during DBS not only should be attributed to the DBS target structure, surgical trajectory, and stimulation

6. We do not have enough space to adequately characterize the accounts in Table 2 concerning the potential DBS-induced effects on the self. Rather, we aim to examine a patient's postoperative phenomenological experience of first-personal or subjective change, especially responses, or feelings of, self-estrangement.

7. Though not necessarily all those listed in Table 2.

Table 2. Survey of the existing model of DBS-induced effect on the self.

Central concept of ethical significance given impact of DBS	Discussed by	DBS impacts characterized by	Quote	Model of self
Autonomy and related concepts	Synofzik and Schlaepfer (2008)	The “level” and “extent” of changes to naturalistic notion of personality	“The ethically decisive question is not whether DBS alters personality or not, but whether it does so in ‘a good or bad way’ from the patient’s very own perspective.” (1514)	Naturalistic model of self as the “objective, biological-cognitive representational system with special characteristic self-representational capacities” (1513)
Autonomy and related concepts	Schermer (2011)	Perceived changes to narrative identity	“[W]hether or not the patient himself perceives the changes in his personality, mood, behavior, or cognition brought about by DBS as disruptive of his personal narrative identity.” (2)	Narrative identity
Autonomy and related concepts	Gilbert (2013a, 2015, 2017)	Loss of control and powerlessness	“Postoperative self-estrangement may enhance or restore one’s control over one’s life or illness. However, in some cases, DBS radical modifications of the self may lead to a loss of control or experiencing feelings of powerlessness.” (109)	#
Autonomy and related concepts	Mackenzie and Walker (2015)	Autonomy competence	“This distress, in our view, points to threats to autonomy rather than to identity or authenticity, as the salient concern underlying narratives of self-alienation.” (390)	Relational, narrative understanding of identity and autonomy
Authenticity and related concepts	Johansson et al. (2011)	Personality changes and impacts on authenticity	“The concept of authenticity ... provides a means to entangle both philosophically and generally held intuitions regarding normative claims connected to personality changes.” (2)	Normative thesis of authenticity

Authenticity and related concepts	Kraemer (2013)	Felt-authenticity and felt-alienation	"For some, alienation can be brought about by neurointerventions because patients no longer feel like themselves. But, on the other hand, it seems alienation can also be cured by DBS as other patients experience their state of mind as authentic under treatment and retrospectively regard their former lives without stimulation as alienated." (483) "Cerebral implants are a unique form of biographical disruption ... [T]he patient loses control over managing the illness and experiences significant changes in personality." (1850) "Neuromodulation via implanted electrodes can influence narrative identity directly and indirectly." (2) "Stimulating the brain ... may alter a range of mental states critical to thought, personality and behavior. This can disrupt the integrity and continuity of the psychological properties that constitute the self and one's experience of persisting through time as the same person" (289) "DBS may ... influence mental states critical to personality to such an extent that it affects an individual's personal identity ... [This] raises a number of ethical and legal questions. ... [I]nduced changes ... [may] result in damage caused by undesirable or even deviant behavior. Disruptions in psychological continuity can in some cases also have an effect on an individual's mental competence." (527)	Identification/endorsement with felt-authenticity and felt-alienation
Identity and related concepts	Gisquet (2008)	Changes in personality and loss of control over managing one's life and illness		Biographical
Identity and related concepts	Focquaert and De Ridder (2009)	Changes in personality and self-perception		Narrative identity
Identity and related concepts	Glannon (2009)	Changes in thought and personality		Narrative identity
Identity and related concepts	Klaming and Haselager (2010)	Disruptions of psychological continuity impact on patient competence and responsibility		Psychological criteria of personal identity

(Continued on next page)

Table 2. Survey of the existing model of DBS-induced effect on the self. (Continued)

Central concept of ethical significance given impact of DBS		DBS impacts characterized by		Quote	Model of self
Identity and related concepts	Witt et al. (2013)	Patient's core attitudes		"Ethical evaluation of deep brain stimulation as treatment for Parkinson's Disease is complicated by results that can be described as involving changes in the patient's identity. The risk of becoming another person following surgery is alarming for patients, caregivers and clinicians alike." (499)	Foundational-function model: self as a set of core attitudes
Identity and related concepts	Mecacci and Haselager (2014)	Psychological maladaptations and conceptual schemes concerning the relationship between mind and brain		"We hypothesize that the frequently reported maladaptations might be partially caused by a conceptual emphasis on 'braincentric' materialism." (31)	Embodied embedded stance toward the mind-brain relationship
Identity and agency	Schechtman (2010)	Narrative identity and agency /disruption of the narrative flow		"Stimulation-related psychological and personality changes represent a threat to personal identity and agency." (133); "DBS can pose a threat to identity by threatening narrative." (139)	Narrative self-constitution
Identity and agency	Baylis (2013)	Disruption of the balance between how a person sees and understands herself and how others see and understand her		"From the perspective of relational personal identity, when DBS dramatically disrupts the narrative flow, this disruption is best examined through the lens of agency." (514)	Relational narrative identity
Identity and agency	Lipsman and Glannon (2013)	Personal identity and a sense of free agency		"Brain implants . . . have significant implications for what it means to persist as the same person and be the source of one's thoughts and actions." (465)	Neurobiology of identity (narrative and numerical) and identification (Frankfurt)

Identity and agency	Dings and de Bruin (2016)	Aspects of the self—embodied, experiential, affective, intersubjective, psychological/cognitive, narrative, extended, and situated	“Our aim in this paper is to develop a pattern theory of the self, and to explain how this theory can be applied at the level of pattern types and pattern tokens.” (fn 8, 158)	Pattern theory of self
Identity and agency	De Haan et al. (2013; 2015)	Patients experience a richer field of affordances and act more flexibly on these new affordances	“It turns out that patients may experience profound changes as the result of DBS treatment. It is not just the symptoms that change; patients rather seem to experience a different way of being in the world.” (2013, 1)	Enactive, affordance-based model

parameter, but also should account for patient history, disease attributes, and other forms of treatment adaptations such as medication adjustments and psychotherapy.

At this point in time, it is relatively difficult to isolate the cause of these postoperative changes, though they have been associated with DBS. To the best of our knowledge, no neurobiological studies claim that postoperative personality changes can be predicted solely on the basis of DBS itself or an exclusive neurobiological cause. Even in a tragic case where a patient implanted with DBS died by suicide, an indirect causal explanation was used in the legal case to argue that postoperative changes are “more likely than not to have been due in significant but unquantifiable measure to the DBS” (Dillon 2014).

A similar relationship is seen in Parkinson’s disease patients who develop compulsive behaviors or impulse control disorders (ICD) (e.g., compulsive gambling, shopping, and eating) associated with dopamine replacement therapy. As seen during our interviews, many patients reported self-changes due to medication. This correlates with other findings that show that almost 17% of individuals with PD who are treated with dopamine agonists (DA) will develop an ICD (Ambermoon et al. 2011). There is strong evidence that DA plays an important causal role: These behaviors tend to emerge soon after commencing the medication or increasing doses, and they often resolve when the medication is stopped, as some of our patients reported. There is also a plausible explanation for how dopaminergic medications would lead to compulsive behaviors. The medication only plays a partial causal role: the overwhelming majority of individuals do not develop these disorders. There are also predictable individual differences that identify the likelihood of developing a compulsive behavior, such as having a personal or family history of addictive or impulsive behavior. The sorts of behaviors that emerge appear to be heavily influenced by social factors: Women tend to engage in compulsive shopping and eating, while men are more likely to develop pathological gambling or hypersexuality.

In short, this work does not advocate that DBS alone directly causes potential personality changes.

LIMITATIONS OF THE STUDY

There are a number of limitations in this study. It is important to clarify what the study was, and was not, doing. There is concern with the lack of data concerning first-personal phenomenological reports or assessments of neural implants, which this article in some sense seeks to address. Connected to this point is the concern that no generalizable conclusions can be drawn from such limited data. While looking at the phenomenology of DBS might be a useful tool for describing the lived experiences of implanted patients, it remains severely impoverished as a theory for explaining it (Sholl 2015). However, we are not attempting to draw generalizable

conclusions on the basis of numbers, but rather, we aim to examine phenomenological first-personal reports to inform understandings of the impacts of DBS on patients’ self, with a focus on self-estrangement.

First, it should be recognized that drawing on subjective or first-personal phenomenological accounts of how a person feels about or experiences their implant does not provide us with enough context to assess the (objective) accuracy of these accounts. Estrangement is not necessarily self-perceived. As other studies have demonstrated, relatives are often more sensitive to alterations in self than the patients themselves (Pham et al. 2015). In addition to what we discussed in the previous section, Patient 03 reported, “I don’t feel different at all. Some people said to me that I am a bit different.” Correspondingly, Patient 06 reported, “I think I have been causing a bit of problems in my relationships.” Also, the epistemic role of the first-personal perspective may be limited, particularly in the case of induced mania. We are not questioning the what-it’s-like-ness but rather the consistency of the narration. As family members pointed out to Patient 04, “They said they don’t recognize me . . . I am so impulsive and seem to change my mind all the time.” Here it is not the experiential-qualitative character of being manic which is problematic, but rather the consistency of the narrative account. Families and social context are an essential measurement of how patients are experiencing potential estrangement, even if patients do not perceive it. An extended study would not only involve interviewing the implanted patients, but also their close relatives. In the current study, patients were asked whether their relatives mentioned any postoperative changes, but systematically interviewing patients’ relatives would have likely generated more data.

Second, and more importantly, our study merely asked patients to report on their perception of self-change. As such, it provides a limited amount of information about patients’ uptake and adaptation over time. As such, there is insufficient evidence to draw conclusions about how the implants affect autonomy and identity and consequently to draw conclusions about the impacts on autonomy and identity. An extended version of the study should also include interviews made before the intervention, and at least two follow-ups; this would add important insights regarding the degree of “self-deception” of patients when remembering their state prior to surgery. Further, the study should include focus on the patient’s engagement with the world and his or her implant, in addition to reporting on perception of self-change.

Despite these identified limitations, we strongly believe that we can draw some robust and common findings from the patient postoperative narratives, as we have done in the preceding, and on the basis of these findings make some conclusions, as summarized in the following. Further, exploring patient’s first-personal experience of DBS can inform and guide patients through decision-making processes leading to implantation, and can also answer questions of patients currently experiencing self-estrangement phenomenon.

CONCLUSIONS

Subjective self-reports from PD patients with DBS help us to understand some aspects of potential postoperative self-estrangement. The way patients perceive themselves through pathology will likely dictate the way they will experience potential DBS-induced self-estrangement; self-perception through pathology will likely dictate degrees of whether patients self-perceive DBS as something that is restorative. The notion of self-estrangement seems to exist in association with certain common qualitative characters: (1) loss of control and (2) distorted perception of capacities. The first is mostly associated with a deteriorative sense of the self, and the second is largely related to a restorative one. Most implanted patients we interviewed experienced a shift in their self-perception, mostly in a restorative sense, especially during calibration. Some feelings of deterioration were experienced in relation to powerlessness, which resulted in severe harm in one case. This evidence supports the hypothesis that postoperative feelings of powerlessness play a crucial role in causing harm (Gilbert 2013a, 2015a). This study demonstrates that DBS, as a whole, increases autonomous restorative power over one's self, rather than a deterioration of the self. This is anecdotally supported by our interviews with patients who reported a sensation of empowerment. The explanation for this may reside in the concept of embodiment, where the device is felt to become part of the individual, rather than as a foreign despot exerting control (Amadio and Boulis 2015).

It appears from these clusters that most patients experience a proportionally restorative sense of the self. This evidence justifies the claim that, generally speaking, DBS is not a threat to personal, but some patients might not experience well any form of estrangement. Patients would benefit from being informed ahead of any potential risks, prior to consenting to being implanted, as in other types of invasive brain intervention (Viaña, Vickers et al. 2017; Gilbert et al. 2014; Viaña, Bittlinger et al. 2017; Gilbert 2015b; Bretzner et al. 2011; Gilbert, Vranic, and Hurst 2013; Gilbert 2014; Gilbert et al. 2015; Vranic & Gilbert 2014; Gilbert & Cook 2015; Gilbert 2017; Gilbert & Dodds 2013; Gilbert & Focquaert 2015; Gilbert & Vranic 2015).

This study highlights the importance of the first-personal perspective and subjective assessments when considering the impacts of implants and the need for more assessments. More significantly, however, we argue that further and more fuller phenomenological exploration of how patients respond to their neural implants is needed in order to draw conclusions about the impacts of DBS on autonomy and identity. This would involve interrogating patients' agency over time so that we can make an assessment of whether initial disruptions, feelings of self-estrangement, and failures in decision making are short-term or long-term phenomena. Furthermore, this would involve assessing how patients live with their implants, with a focus on whether the implant facilitates or hinders their capacities to engage in the world.

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APPENDIX: SEMISTRUCTURED INTERVIEW SCRIPT

These are examples of generic questions. They are an indication of the structure to be followed during the interviews, rather than the actual questions to be asked to patients. The choice of words, terminology, or languages may change slightly for each patient.

1. Potential questions regarding postoperative sense of the self.
 - i. What was it like to live without the deep brain stimulation (DBS) device? Did you feel comfortable in yourself with your medical condition? How did you feel that your medical condition affected your life?
 - ii. What is it like to be implanted with DBS? Do you feel any significant difference from before the device compared to after it was implanted?
 - Please provide some examples. Did you expect to find differences or changes prior to the operation?
 - iii. Have others commented on any changes to you (e.g., personality, habits, etc.) since being implanted? If so, do you agree with them? Why or why not?
 - iv. (Depending on previous answers) Do you think you may change/change more in the future as a result of this intervention?
2. Potential questions regarding the sense of control.
 - i. Prior to the implantation of DBS, how would you describe your control over your life? (e.g., through habits, daily activities, etc.)
 - ii. Do you feel the device has increased your autonomy (e.g., making you less dependent on others)? For instance, has it improved your life, control on symptoms? Has it given you back more control over your life?
 - iii. Have others commented that you have better control over your life/symptoms/yourself? Do you agree with them? If not, why not?
 - iv. (Depending on previous answers) If you experienced the device as form of control, does it feel authentic? From your own personal experience, do you see it as a novel control?

A highly tunable dopaminergic oscillator generates ultradian rhythms of behavioral arousal

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Abstract Ultradian (~4 hr) rhythms in locomotor activity that do not depend on the master circadian pacemaker in the suprachiasmatic nucleus have been observed across mammalian species, however, the underlying mechanisms driving these rhythms are unknown. We show that disruption of the dopamine transporter gene lengthens the period of ultradian locomotor rhythms in mice. Period lengthening also results from chemogenetic activation of midbrain dopamine neurons and psychostimulant treatment, while the antipsychotic haloperidol has the opposite effect. We further reveal that striatal dopamine levels fluctuate in synchrony with ultradian activity cycles and that dopaminergic tone strongly predicts ultradian period. Our data indicate that an arousal regulating, dopaminergic ultradian oscillator (DUO) operates in the mammalian brain, which normally cycles in harmony with the circadian clock, but can desynchronize when dopamine tone is elevated, thereby producing aberrant patterns of arousal which are strikingly similar to perturbed sleep-wake cycles comorbid with psychopathology.

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Introduction

Ultradian rhythms with periods ranging from one to several hours have been linked to various aspects of mammalian physiology. Usually superimposed on the 24-hr diurnal or circadian rhythm, ultradian oscillations have been observed in the context of locomotion, sleep, feeding, body temperature, serum hormones, and brain monoamines in species ranging from fruit flies to humans (*Tannenbaum and Martin, 1976; Ibuka et al., 1977; Rusak, 1977; Daan and Slopeema, 1978; Honma and Hiroshige, 1978; Dowse et al., 1987; Rivkees, 2003; van Oort et al., 2007; Dowse et al., 2010; Seki and Tanimura, 2014*). These physiological cycles most frequently exhibit periods of 2–6 hr, adopting harmonics of the 24-hr daily light–dark cycle or the endogenous circadian rhythm, when external timing cues are absent. However, the generation of such ultradian rhythms does not depend on a functional circadian system nor a light:dark cycle. Ultradian locomotor oscillations persist in rodents housed in constant darkness even upon ablation of the suprachiasmatic nucleus (SCN), the site of the master circadian pacemaker (*Ibuka et al., 1977; Rusak, 1977*), or genetic disruption of the circadian clock (*Vitaterna et al., 1994; Bunker et al., 2000*) (*Figure 1A,B*). These ultradian activity cycles may not simply be driven by metabolic demand since the 2- to 3-hr rhythm in foraging activity observed in the common vole persists even in the absence of food (*Gerkema and van der Leest, 1991*). Studies in this species further indicate that one adaptive value of ultradian activity rhythms may lie in the facilitation of social synchrony, which is suggested to reduce predator risk in this species

eLife digest The sleep-wake cycle of mammals is controlled by a ‘circadian clock’ within the brain, which is synchronized to the day–night cycle. However, other aspects of mammalian physiology including alertness and activity levels, as well as appetite and body temperature—fluctuate in cycles that repeat every few hours. These cycles are known as ultradian rhythms, and they may offer survival benefits by enabling potentially risky behaviors, such as foraging, to be coordinated between members of a group.

Despite their widespread nature and the fact that they appear to be conserved in evolution, virtually nothing is known about the molecular basis of ultradian rhythms. Blum et al. have now identified a second internal clock within the brain, which they name ‘the DUO’, and shown that this clock normally works in concert with the circadian clock to regulate daily patterns of activity and alertness.

Experiments in mice revealed that the DUO uses the brain chemical dopamine to generate bursts of activity roughly every four hours. Moreover, it continues to work when the circadian clock has been destroyed. Measurements of dopamine in freely moving mice showed that levels of the chemical fluctuate in synchrony with the animals’ activity levels. Moreover, drugs that flood the brain with dopamine, such as methamphetamine, disrupt the 4-hour cycle by lengthening the period between bursts of activity, whereas drugs that block dopamine receptors have the opposite effect.

As well as revealing a mechanism by which the brain coordinates processes that repeat several times per day, the identification of the DUO could also provide insights into the biological basis of psychiatric disorders. Conditions such as schizophrenia and bipolar disorder are often accompanied by disturbances in patterns of activity and rest. While these have previously been attributed to the disruption of circadian rhythms, there is little direct evidence for this, which raises the possibility that these changes might instead reflect the disruption of ultradian rhythms.

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(*Gerkema and Verhulst, 1990*). However, despite their prevalence and hypothesized biological significance, ultradian locomotor rhythms have received little research attention, likely owing to their frequently masked expression and unstable periodicity in contrast with circadian activity rhythms (*Ruis et al., 1987; Schibler, 2008*) (*Figure 1C,D*).

In addition to ultradian oscillations, methamphetamine-induced rhythms of locomotor activity occur in the absence of a functional circadian clock. When provided in the drinking water, methamphetamines (Meth) induce a daily activity bout in addition to the expected circadian rhythm (*Honma et al., 1986*). This Meth-dependent component—which typically adopts a period in the circadian range—is not abolished upon SCN lesion nor by genetic disruption of circadian clock function (*Honma et al., 1987; Mohawk et al., 2009*). It was thus concluded that a methamphetamine-sensitive circadian oscillator (MASCO) outside the SCN exists which is capable of driving daily cycles of locomotor activity (*Tataroglu et al., 2006*). Despite the longstanding recognition of ultradian and Meth-dependent rhythms, the underlying cellular and molecular identity of the oscillator(s) driving them is unknown.

Here, we provide evidence for a highly tunable dopaminergic ultradian oscillator (DUO) which is continuously operative in the mammalian brain and which, together with the circadian clock, orchestrates the daily pattern of arousal. Our data suggest that dopamine acts as both the principal oscillator output as well as an integral component of the DUO, determining oscillator period. Our findings further indicate that the previously described MASCO represents a long-period manifestation of the DUO resulting from elevated dopamine tone. Importantly, our data support an intriguing proposition: that DUO, rather than circadian clock, dysregulation critically contributes to the sleep-wake abnormalities associated with psychopathology.

Results

Dopamine transporter deficiency results in ultradian locomotor period lengthening

To gain insights into the mechanistic basis of ultradian locomotor rhythm generation, we considered that locomotor activity is associated with an awakened state (*Welsh et al., 1988*) and consequently,

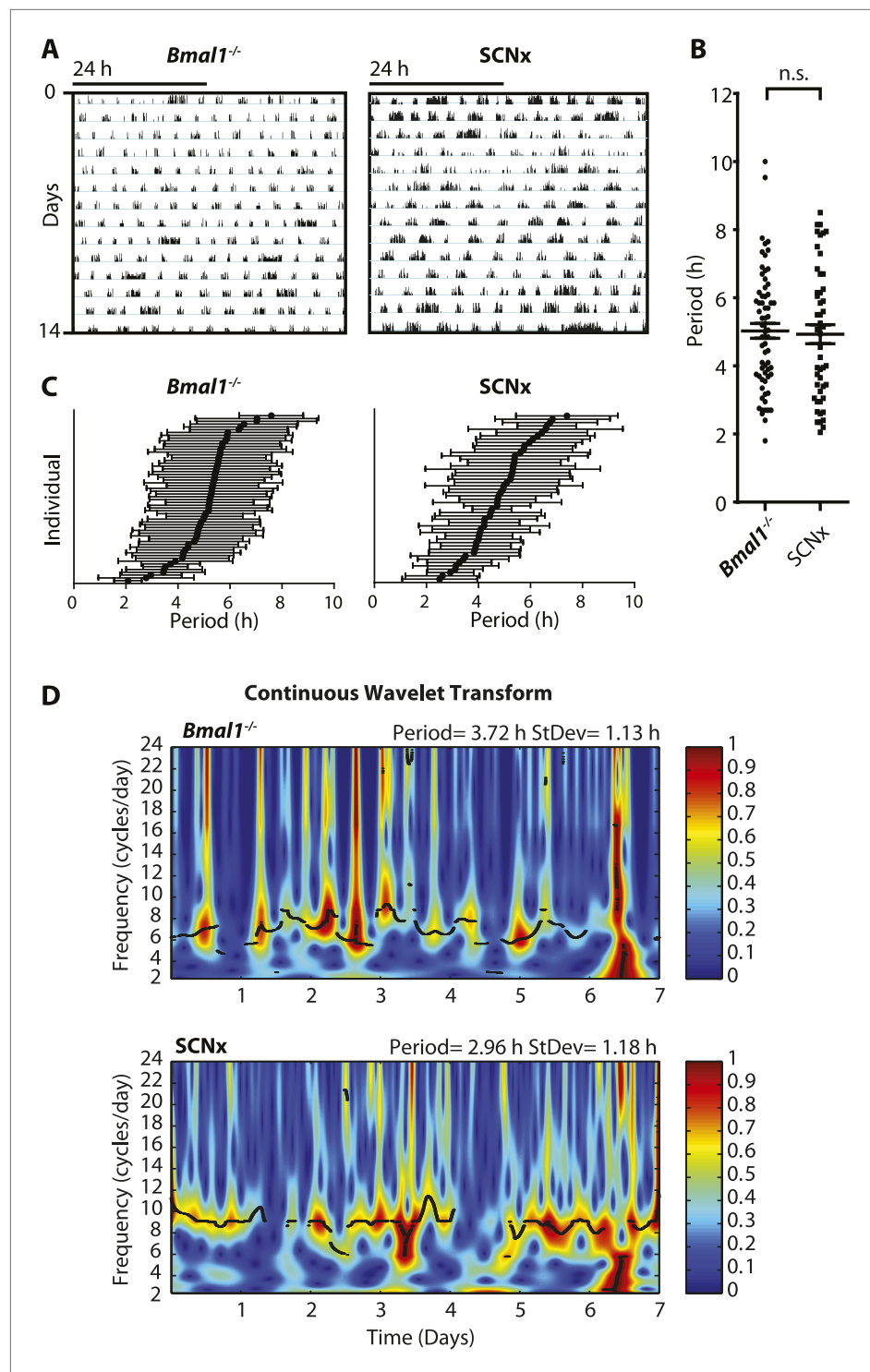


Figure 1. Inter- and intra-animal variability of ultradian activity rhythms across time in circadian incompetent mice. (A) Representative double-plotted actograms of running wheel activity in SCN-lesioned (SCNx) and *Bmal1*^{-/-} mice in DD. (B) Dot plot of locomotor period length in DD based on Lomb-Scargle periodogram analysis of seven consecutive days of activity recording (N = 65 for *Bmal1*^{-/-} and N = 48 for SCNx; $t_{111} = 0.2785$, $p = 0.78$, unpaired t-test). (C) Intra-animal period variability expressed as mean $\pm$ SD for each animal, ranked according to mean period length derived from continuous wavelet transforms (CWT) for the 1–12-hr frequency range (same animals and timespans for calculation as in B). (D) CWT-heatmaps showing decibel scaled and normalized amplitude of oscillations according to frequency and time with black traces indicating the ridge of local amplitude maxima.

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the ultradian locomotor rhythms observed in mice that lack circadian clock function (**Figure 1**) could be interpreted as rhythms of heightened wakefulness or arousal. In mammals, a key role in arousal promotion has been attributed to distinct monoaminergic neuronal populations located in the upper brainstem and midbrain (**Brown et al., 2012**). While altering extracellular levels of the arousal-associated monoamines serotonin, norepinephrine, or histamine by genetic manipulation has only limited effects on locomotion (**Thomas and Palmiter, 1997; Bengel et al., 1998; Xu et al., 2000; Parmentier et al., 2002; Zhao et al., 2006**), depleting the brain of dopamine (DA) profoundly abrogates locomotor activity (**Zhou and Palmiter, 1995**). Moreover, increasing extracellular DA levels induces hyperlocomotion (**Giros et al., 1996**) and lengthens the time spent awake (**Wisor et al., 2001**). We therefore speculated that altering DA tone may affect ultradian rhythm generation. To test this, we examined running wheel activity in mice carrying a disruption in the *Slc6a3* gene, which encodes the dopamine transporter (DAT). *Slc6a3*^{-/-} mice exhibit hyperdopaminergia due to the lack of DAT-mediated DA reuptake into dopaminergic neurons, leading to a hyperactivity phenotype (**Giros et al., 1996; Gainetdinov et al., 1998**). As the presence of the circadian clock and/or a light:dark cycle frequently masks ultradian activity rhythms (**Schibler, 2008**), we assessed the locomotor behavioral consequences of DAT elimination in the absence of the master SCN circadian pacemaker. To do so, we electrolytically lesioned the SCN of *Slc6a3*^{-/-} mice and their wildtype littermates and monitored their running wheel behavior in constant darkness (DD). While control mice (SCNx-*Slc6a3*^{+/+}) exhibited ultradian activity rhythms with the expected ~4-hr period, SCNx-*Slc6a3*^{-/-} mice showed rhythms whose periods were three times longer (**Figure 2A,B**). Analysis of mice that were deficient for both DAT and the essential clock component BMAL1 (*Bmal1*^{-/-}, *Slc6a3*^{-/-}) corroborated this finding. *Bmal1*^{-/-}, *Slc6a3*^{-/-} mice exhibited ~12–14-hr rhythms in locomotor activity, largely phenocopying the SCNx-*Slc6a3*^{-/-} mice, while their *Bmal1*^{-/-}, *Slc6a3*^{+/+} littermates showed ~4-hr periods as expected for isodopaminergic mice lacking circadian clock function (**Figure 2C,D**). Together, these results suggest that DAT removal markedly increases ultradian cycle length. Alternatively, the ~12-hr rhythms observed in SCNx-*Slc6a3*^{-/-} and *Bmal1*^{-/-}, *Slc6a3*^{-/-} animals may originate from an independent oscillator, one that is activated by DAT elimination, while the short period ultradian oscillator that operates in DAT intact, SCNx or *Bmal1*^{-/-} animals is disengaged or otherwise obscured.

The psychostimulant methamphetamine lengthens ultradian locomotor period

In order to corroborate that DAT removal indeed lengthens the period of the ultradian activity cycles, we took into account that DAT-mediated DA uptake can be reversed by the selective action of the psychostimulant methamphetamine (Meth) (**Howell and Kimmel, 2008**). Because Meth leads to increased extracellular DA concentrations as in the case of *Slc6a3* gene disruption, we speculated that Meth treatment would result in a, possibly gradual, period lengthening of the ultradian locomotor rhythms. Indeed when we treated *Bmal1*^{-/-} animals with increasing concentrations of Meth via drinking water in DD, we observed a gradual lengthening of the initial ~4-hr locomotor oscillations and this was accompanied by a corresponding increase in activity bout length (**Figure 3A,B**). Of note, the period increase in response to elevating Meth concentrations did not halt in the circadian range, rather, oscillations continued to lengthen with individual animals reaching periods of 100 hr or more (**Figure 3C**). Gradual period lengthening of ultradian locomotor rhythms was also observed in *Bmal1*^{-/-} animals exposed to amphetamine (**Figure 3—figure supplement 1A,B**), a drug similarly targeting DAT (**Howell and Kimmel, 2008**), but with lower efficacy than Meth (**Goodwin et al., 2009**). These results argue that DAT targeting psychostimulants affect an endogenous ultradian rhythm generator by increasing period length. However, due to the mode of delivery (drinking water) and the rhythmic Meth uptake that may in turn result from it, it is conceivable that the Meth-dependent, long-period oscillations are 'driven' by rhythmic drug intake rather than being generated endogenously. To address this possibility, we subcutaneously implanted *Bmal1*^{-/-} mice with osmotic minipumps that continuously infused Meth over a period of 2 weeks. Running wheel analysis in DD of Meth-infused *Bmal1*^{-/-} animals demonstrated a significant ultradian period lengthening upon drug infusion (**Figure 3—figure supplement 1C,D**) suggesting that rhythmic uptake is not required for Meth to exert its period lengthening effect, in line with a previous study performed in rats (**Honma et al., 1987**). The relatively limited change in period observed in this experimental paradigm could be due to the short, 2-week infusion timespan, which is perhaps insufficient to robustly lengthen periods beyond 12 hr (**Figure 3—figure supplement 1D**). Together, these findings support the notion that the long-period oscillations observed

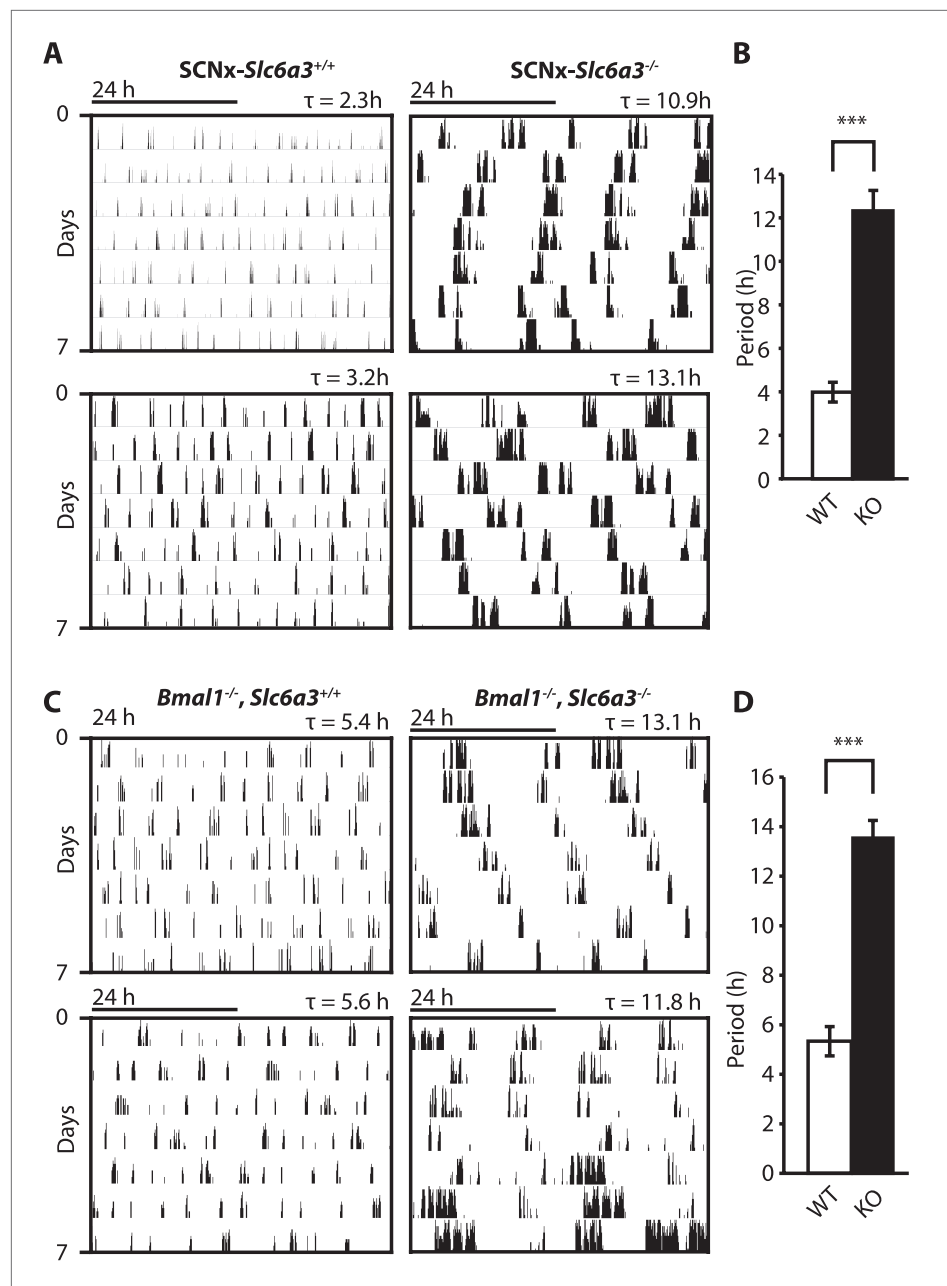


Figure 2. Dopamine transporter knockout alters periodicity of ultradian locomotor rhythms in circadian incompetent mice under constant darkness. **(A)** Representative, double-plotted actograms demonstrating marked lengthening of ultradian locomotor periods in *SCNx-Slc6a3*^{-/-} mice as compared to *SCNx-Slc6a3*^{+/+} littermates. Tau(τ) indicates individual period. **(B)** Period length averages of ultradian activity ($N = 7$; $F_{1,6} = 253.8$, *** $p < 0.0001$, ANOVA) from Lomb-Scargle periodogram analysis of 7-day time-spans. **(C)** Representative, double-plotted actograms demonstrating markedly increased ultradian period lengths in *Bmal1*^{-/-}, *Slc6a3*^{-/-} mice as compared to *Bmal1*^{-/-}, *Slc6a3*^{+/+} mice. **(D)** Period length averages of ultradian activity ($N = 4$; $F_{1,3} = 194.2$, *** $p < 0.001$, ANOVA) from Lomb-Scargle periodogram analysis of 7-day time-spans.

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in Meth-treated animals, and likewise in *Slc6a3*^{-/-} mice, are due to period expansion of an endogenous ultradian rhythm of arousal.

We next aimed to confirm these findings in intact mice. While activity rhythms in the ultradian range are easily discernable in voles and hamsters (Gerkema et al., 1990; van der Veen et al., 2006; Prendergast et al., 2012), the presence of such rhythms in mice or rats is much less obvious and this

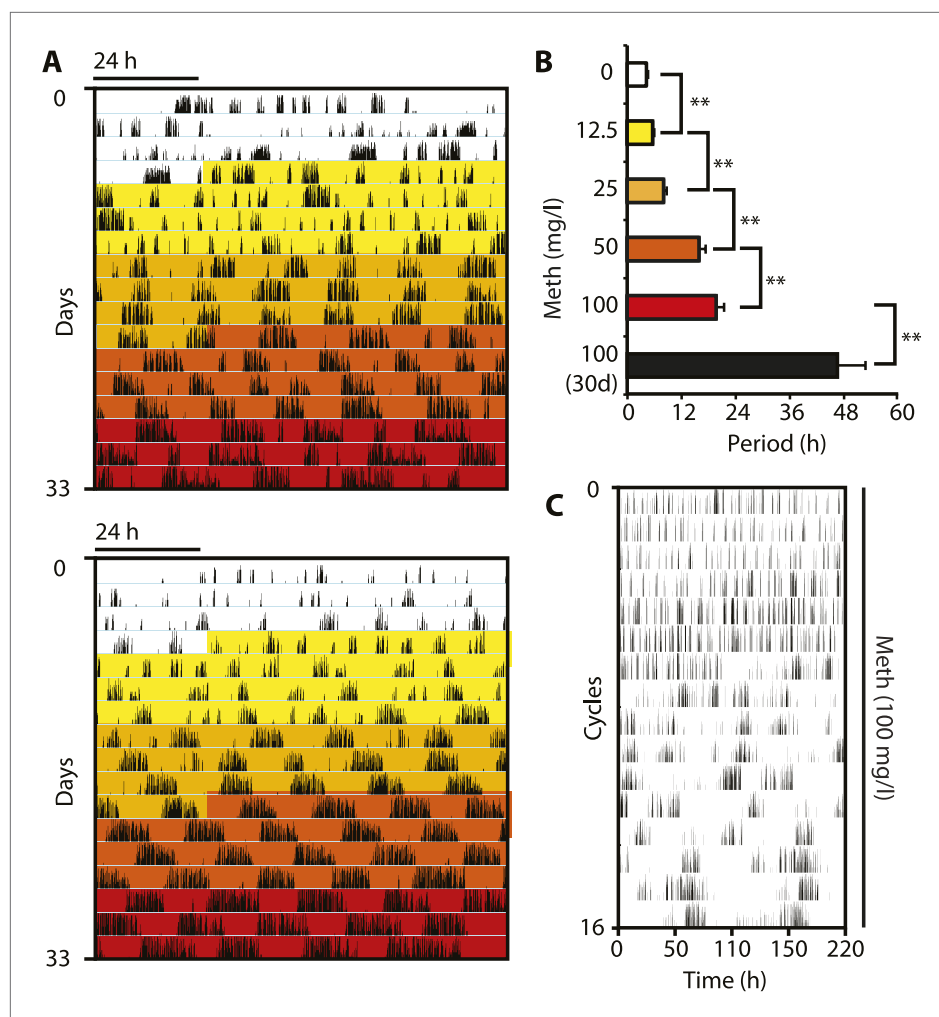


Figure 3. Pharmacological tuning of DAT activity by incrementally increasing methamphetamine concentrations lengthens ultradian locomotor period into the infradian range. **(A)** Representative actograms of Meth-treated *Bmal1*^{-/-} mice in DD. Treatment intervals are highlighted with corresponding concentrations indicated in **(B)**. **(B)** Mean periods from the last 7 days at a given Meth concentration. Repeated measures ANOVA revealed a significant main effect of concentration/time ($F_{5,40} = 34.30$, $p < 0.001$) and significant period lengthening between consecutive concentrations (mean $\pm$ SEM; $N = 9$; $**p \leq 0.005$, planned comparisons; 30 day, 30 day exposure to 100 mg/l). **(C)** Modulo 110-hr actogram of a *Bmal1*^{-/-} animal after extended exposure to Meth revealing an ultra-long activity rhythm.

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The following figure supplement is available for figure 3:

Figure supplement 1. Amphetamine treatment lengthens ultradian locomotor rhythms in *Bmal1*^{-/-} mice.

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has been attributed to masking by the circadian clock (*Schibler, 2008*). Indeed, running wheel activity data from intact mice often do not provide strong indications of ultradian activity rhythms. However, when we recorded ambulatory behavior using telemetry, we frequently detected three, evenly spaced activity bouts during the active (night) phase (**Figure 4A**). The observed ~4 hr peak-to-peak spacing is in line with a previous study on several circadian competent mouse strains where ultradian rhythms with similar period length were detected (*Dowse et al., 2010*). The absence of a clearly discernable ~4-hr rhythmic component during the light portion of the daily LD cycle (**Figure 4A**) is likely due to masking by the SCN and/or light. Unlike WT mice, *Slc6a3*^{-/-} mice never showed a triple-peak activity pattern at night (**Figure 4B**), and spectral density analysis in the ultradian (2–8 hr) range (**Figure 4C**) underscores that rhythm generation is significantly altered in these animals while total daily activity is not (**Figure 4D**). When we provided C57BL/6 mice carrying a telemetry implant with Meth in their

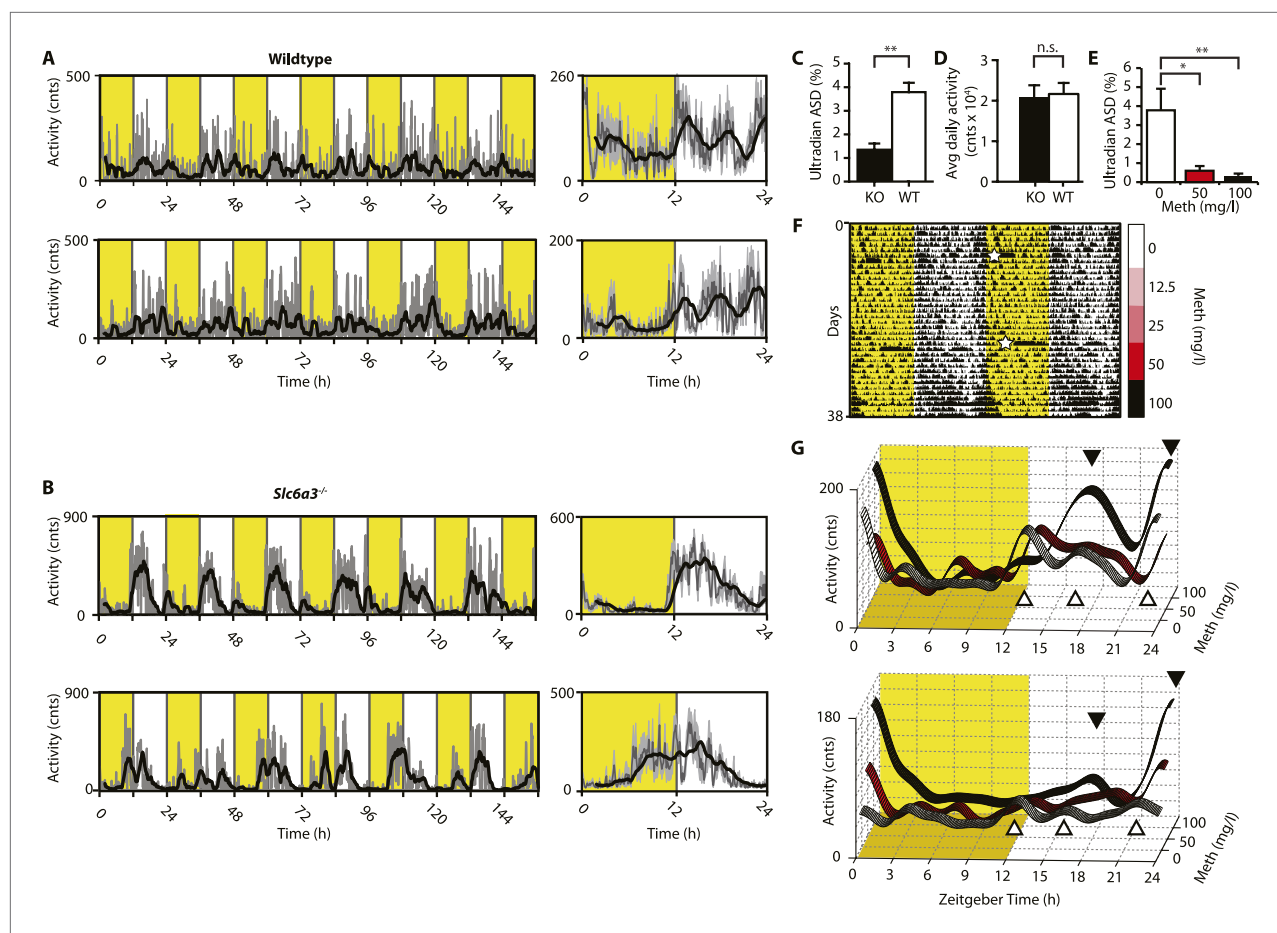


Figure 4. Ultradian activity in SCN-intact *Slc6a3*^{-/-} mice and their wildtype littermates. **(A and B)** Ambulatory activity recorded by telemetry implants across multiple days (left) and averaged over 24 hr (right). Traces represent 2-hr recursive smoothing (black) of the underlying raw DATa (dark grey; SEM envelope, light grey). Areas in yellow indicate lights on. **(C)** Amplitude spectral density in the ultradian range (2–8 hr) is significantly different between *Slc6a3*^{-/-} mice and their wildtype littermates revealing a loss of the ultradian component (mean ± SEM; N = 10; $F_{1,18} = 26.40$, $^{**}p < 0.0001$, ANOVA). **(D)** Although the temporal pattern of locomotion differs between genotypes there is no significant difference in daily activity averaged over multiple days (mean ± SEM; N = 10, $F_{1,18} = 0.1793$, ANOVA). **(E–G)** Addition of Meth to the drinking water of C57BL/6 mice lengthens the night-time activity bouts in a concentration-dependent manner. Averaged daily locomotor activity of individual mice at different Meth concentrations **(G)** derived from the time-span indicated by colored bars next to the representative actogram **(F)** and subjected to Butterworth filtering. The three night-time activity peaks before treatment (white triangles), transform to 2 peaks after exposure to the highest concentration (black triangles). The night-time bout lengthening is also reflected in the reduction of ultradian amplitude spectral density in the 1 to 5-hr range **(E)**, mean ± SEM, N = 7; $F_{2,20} = 8.08$, $p < 0.005$, repeated measures ANOVA; $^{*}p < 0.05$, $^{**}p < 0.01$, post-hoc Bonferroni). White asterisks (in **E**) indicate cage changes.

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drinking water, we observed a gradual lengthening of the interval between the night-time activity peaks (**Figure 4F,G**), resulting in the transformation of the triple peak (**Figure 4G**, white trace and white triangles) into a dual or single night-time activity peak pattern at the highest (100 mg/l) Meth concentration (**Figure 4G**, black trace and black triangles). This was corroborated by spectral density analysis revealing a marked reduction in ultradian frequencies upon Meth treatment (**Figure 4E**). Together, these results indicate that blocking DA reuptake also lengthens ultradian activity bout intervals in circadian competent mice, arguing that an ultradian oscillator is not 'activated' by circadian disruption, but rather continuously operative alongside the circadian timer. As with *Bmal1*^{-/-} mice, prolonged Meth-treatment in intact WT mice can lead to profound period lengthening of ultradian rhythms, often into the circadian (48 hr) range (for examples see Figures 5E, 7F, 9B).

The antipsychotic haloperidol shortens ultradian locomotor period

Given that both DAT disruption and Meth treatment elevate extracellular DA and concurrently lengthen ultradian rhythm period, we speculated that manipulations aimed at lowering DA tone

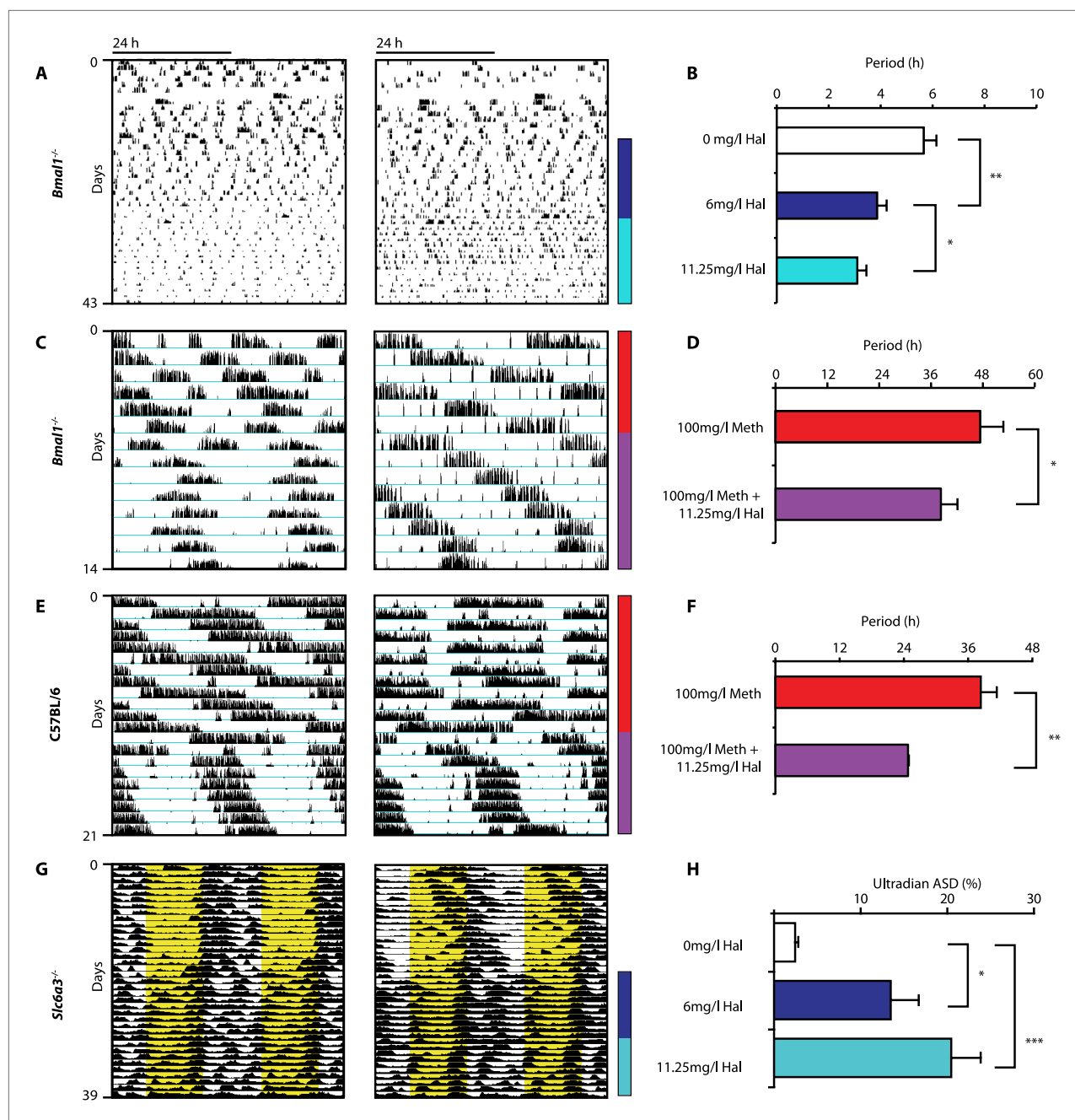


Figure 5. Haloperidol shortens circadian-clock-independent locomotor rhythms. Representative actograms with Hal treatment periods indicated by colored bars (left); bar graphs indicate corresponding locomotor period (right). (A) Increasing concentrations of Hal provided in the drinking water gradually shortens the endogenous ultradian activity rhythms of *Bmal1*^{-/-} mice in DD (B, mean $\pm$ SEM, N = 12; $F_{2,10} = 14.36$, $p < 0.0001$, repeated measures ANOVA; * $p < 0.05$ and ** $p < 0.01$, planned comparison ANOVA). (C and E) Hal shortens the infradian rhythms in Meth-treated *Bmal1*^{-/-} mice (D, mean $\pm$ SEM, N = 9; $F_{1,8} = 2.357$, * $p < 0.05$ ANOVA) and WT mice (F, mean $\pm$ SEM, N = 9; $F_{1,8} = 3.525$, ** $p < 0.01$, ANOVA) in DD. (G) Hal treatment increases the frequency of temperature fluctuation in *Slc6a3*^{-/-} mice under LD measured by telemetric implants. (H) Changes of amplitude spectral density in the ultradian range (2–8 hr) in response to increasing Hal concentrations (mean $\pm$ SEM; N = 8; $F_{2,7} = 14.74$, repeated measures ANOVA, * $p < 0.05$, *** $p < 0.0005$, post-hoc Bonferroni). For all experiments, periods are calculated based on the running wheel activity during the last 7 days of treatment at the indicated Meth/Hal concentration.

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should conversely lead to period shortening. We therefore provided *Bmal1*^{-/-} mice in DD with the antipsychotic drug haloperidol (Hal) in their drinking water. Hal selectively blocks the DA receptor D2 (DRD2) (Strange, 2008), which is expressed on postsynaptic target sites of DA neuronal projections

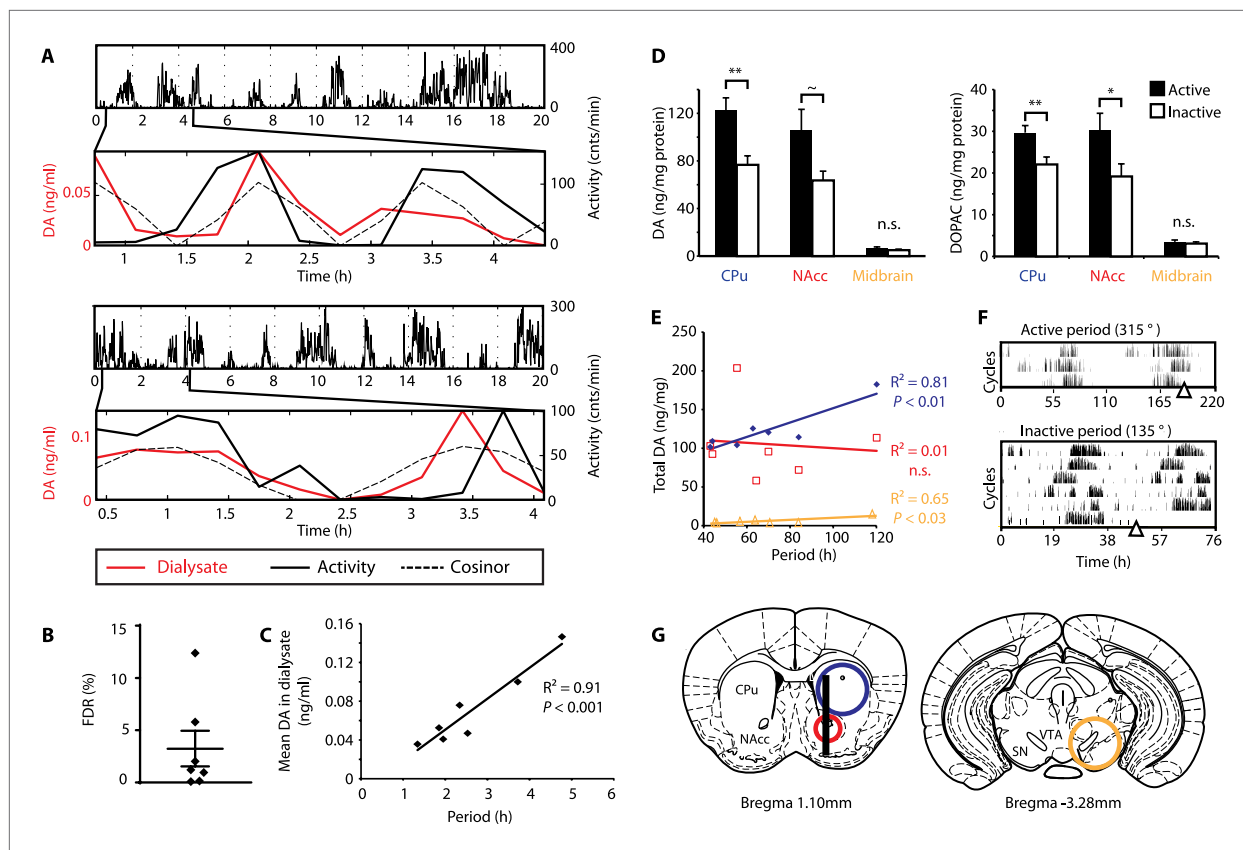


Figure 6. DA fluctuations correlate with ultradian locomotor behavior in *Bmal1*^{-/-} mice. **(A)** Two representative examples of in vivo striatal microdialysis in *Bmal1*^{-/-} mice. Upper: locomotor activity as measured by beam breaks. Lower: DA dialysate concentration measured at 20-min intervals (red trace) plotted alongside the corresponding locomotor activity (solid black trace). Cosinor (dotted line) was computed from the 20 hr of locomotor activity following dialysate sampling. **(B)** False discovery rate of the fit between the DA profiles and corresponding cosinors (mean ± SEM, N = 7). **(C)** Linear regression analysis of period length vs mean DA concentration, dots representing individual animals. **(D)** Tissue punches of CPu, NAcc, and midbrain were analyzed for DA and DOPAC content in animals sacrificed during their active (■) vs their non-active (□) phase (mean ± SEM; active phase, N = 7, inactive phase, N = 6; * $p < 0.05$, ** $p < 0.01$, ~ $p = 0.066$, ANOVA). **(E)** Linear regression for period vs DA content in animals sacrificed during the active phase revealed significant correlations for the CPu and midbrain. **(F)** Representative actograms displaying activity rhythms of Meth-treated *Bmal1*^{-/-} mice used for tissue collection. Triangles indicate collection time points (in °), with locomotor activity bout onset set to 180°. **(G)** Illustrations of coronal mouse brain sections (Paxinos and Franklin, 2001) indicating position of the active membrane (black bar) and tissue punch placements (circles, colors correspond to labels in D and E).

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The following figure supplement is available for figure 6:

Figure supplement 1. Rhythms of extracellular DA in the striatum of freely-moving *Bmal1*^{-/-} mice.

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but also presynaptically as an autoreceptor (Schmitz et al., 2003). Importantly, when given chronically as in our case, Hal has been reported to electrically silence midbrain DA neurons (White and Wang, 1983) and to markedly lower extracellular DA levels in the striatum/nucleus accumbens regions in rats (Lane and Blaha, 1987; Ichikawa and Meltzer, 1991). As predicted, *Bmal1*^{-/-} mice responded with successive locomotor period shortening to increasing concentrations of Hal (Figure 5A,B). We also observed Hal-mediated shortening of the long-period behavioral rhythms in *Bmal1*^{-/-} and wild-type mice treated concurrently with Meth (Figure 5C–F). A period shortening effect of Hal could also be discerned from the core body temperature fluctuations of *Slc6a3*^{-/-} mice, which increased in frequency (Figure 5G). This response, which mirrored the locomotor behavioral response (not shown), was concentration dependent and spectral density analysis confirmed a successive increase of the ultradian component upon Hal exposure (Figure 5H). Together, these data strongly support the hypothesis that both the ultradian rhythms observed in wildtype and *Bmal1*^{-/-} mice and the long-period rhythms previously attributed to the MASCO are driven by the exact same oscillatory mechanism.

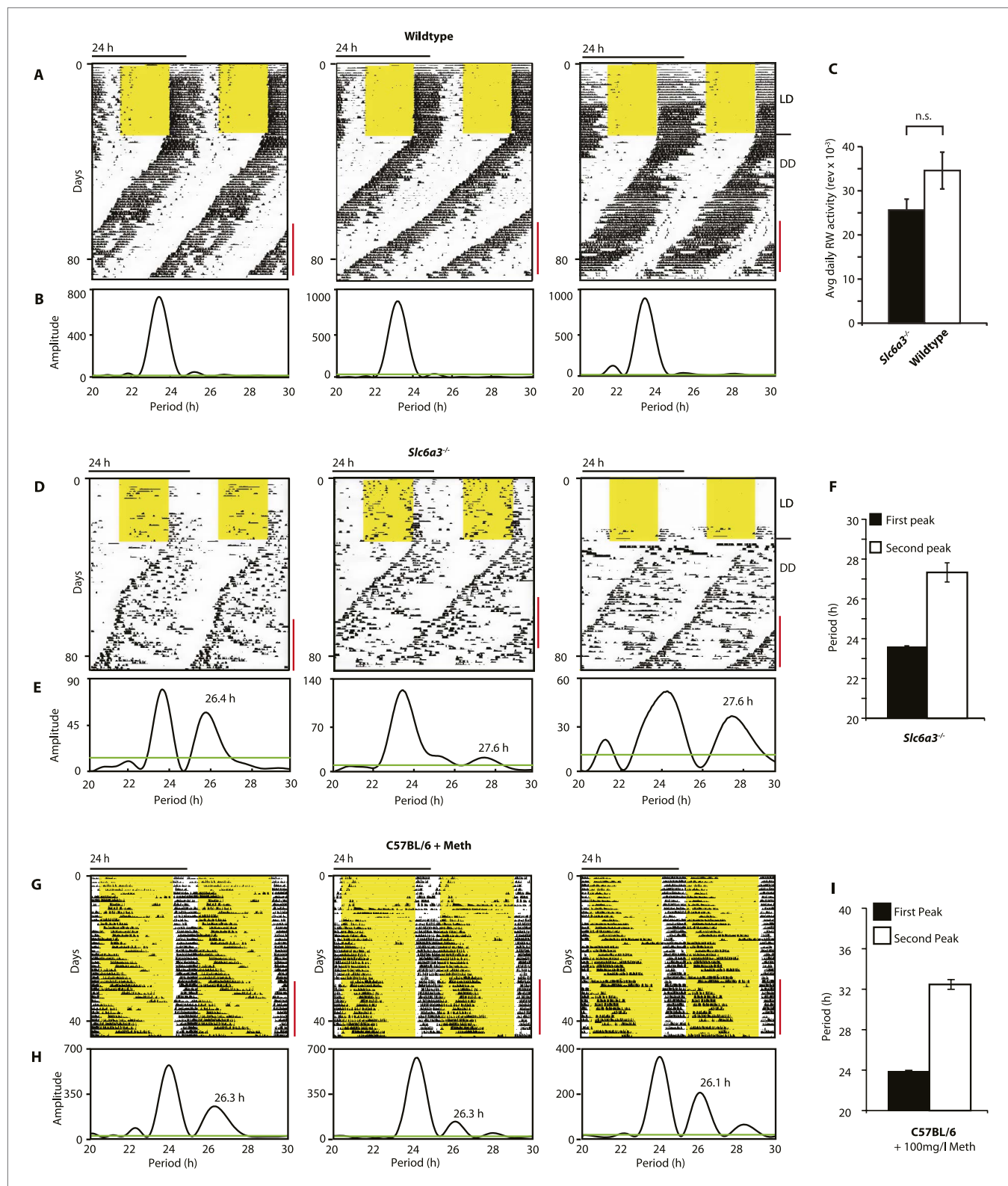


Figure 7. *Slc6a3*^{-/-} mice show a second rhythmic locomotor activity component. Representative actograms displaying daily running wheel activity of *Slc6a3*^{+/+} (A), *Slc6a3*^{-/-} mice (D) and C57BL/6 mice on Meth (G). (B, E and H) Lomb-Scargle periodograms generated from the time-span indicated by red bars, in (A, C, G), respectively. (C) There is no significant difference between genotypes in daily activity averaged over the time-span of analysis (mean ± SEM; N = 6, $F_{1,10} = 1.848$, ANOVA) (F and I) Average periods of the highest 2 periodogram peaks for *Slc6a3*^{-/-} mice (E, mean ± SEM, N = 6)

Figure 7. Continued on next page

Figure 7. Continued

and C57BL/6 mice on Meth (H, mean $\pm$ SEM, N = 9, Meth-treatment started on day 1 of the recordings). Areas in yellow indicate lights-on. Green line in the periodograms indicates the confidence threshold for rhythmicity ($\alpha = 0.01$).

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The following figure supplement is available for figure 7:

Figure supplement 1. The SCN of *Slc6a3*^{-/-} mice is unperturbed.

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As altering extracellular DA is a common denominator of all three manipulations—DAT elimination, (meth) amphetamine, and haloperidol treatment—these findings collectively suggest that DA tone determines ultradian period. Given that DA is known to mediate arousal/wakefulness (Brown et al., 2012), it appears plausible that DA also serves as principal oscillator output, driving rhythms in arousal. We thus hypothesized that extracellular DA must oscillate in synchrony with the observed activity rhythms.

Extracellular DA fluctuates in synchrony with ultradian activity cycles

To test this hypothesis, *Bmal1*^{-/-} mice were unilaterally implanted with a microdialysis probe positioned along the ventro-dorsal extent of the right striatum (Figure 6G), a site heavily innervated by DA neurons. Mice were kept under constant dim red light (<5lux) and ultradian activity rhythms were monitored using infra-red beam breaking. The animals showed the expected short period rhythms in locomotor activity throughout the experiment (Figure 6A), and analysis of dialysates revealed that extracellular DA levels fluctuated concordantly with the activity cycles (Figure 6A and Figure 6—figure supplement 1, compare solid red and black traces). Importantly, we generated a model oscillation using the cosinor method from locomotor rhythms recorded for 20 hr after dialysate sampling with no investigator present and compared it to the DA fluctuations observed. The goodness of fit between the cosinor and the DA profiles indicated by the sum of squared errors (SSE = 0.050 ± 0.027 , mean $\pm$ SEM, N = 7) suggests that the dialysate sampling procedure itself did not perturb the generation of the endogenous ultradian activity cycles. To determine the statistical significance of the observed agreement between the cosinor and the DA trace, we randomly permuted the individual time points of the DA trace and determined the percentage of permuted traces with an equal or better fit to the cosinor in comparison to the observed DA fluctuation. On average, only $3.2 \pm 1.7\%$ of 100,000 permuted DA profiles correlated as well or better than the experimentally observed DA measurements (Figure 6B), confirming that extracellular DA fluctuates in synchrony with the ultradian activity cycles. Of particular note, linear regression revealed a highly significant correlation between mean DA concentration in the dialysate and ultradian locomotor period in the *Bmal1*^{-/-} animals we tested (Figure 6C), which again supports a role of (extracellular) DA as a period determinant of the ultradian activity cycle.

As our findings suggest that the observed >24-hr activity rhythms are due to period lengthening of the ultradian oscillations, we similarly expected DA levels to fluctuate in synchrony with the activity cycles in Meth-treated animals. To test this, we measured DA content in tissue punches of Meth-treated *Bmal1*^{-/-} mice from the dorsal (caudate putamen, CPu) and ventral (nucleus accumbens, NAcc) striatum as well as the ventral midbrain, which includes both the substantia nigra (SN) and the ventral tegmental area (VTA) (Figure 6G). For punch collection, animals were sacrificed during their active and inactive phases, respectively (Figure 6F). We detected significantly higher levels of DA as well as its immediate metabolite, 3,4-dihydroxyphenylacetic acid (DOPAC), in tissue extracts of the CPu during the animal's active phase (Figure 6D). There was also a significant increase in DOPAC levels and a trend towards elevated DA ($p = 0.066$) during the active period in the NAcc, while extracts from the midbrain region, which contains the cell bodies of the striatal dopaminergic afferents, exhibited no detectable change (Figure 6D).

We also found a significant correlation between locomotor period and DA content in CPu and mid-brain punches collected during the active phase (Figure 6E), again consistent with a role for DA as a period determinant of ultradian oscillations.

SCN-intact *Slc6a3*^{-/-} mice show two components of rhythmic activity

As *Slc6a3*^{-/-} mice lack the triple peak night-time activity pattern that is characteristic of wild-type mice, we subjected *Slc6a3*^{-/-} mice to long-term running wheel activity monitoring to examine their

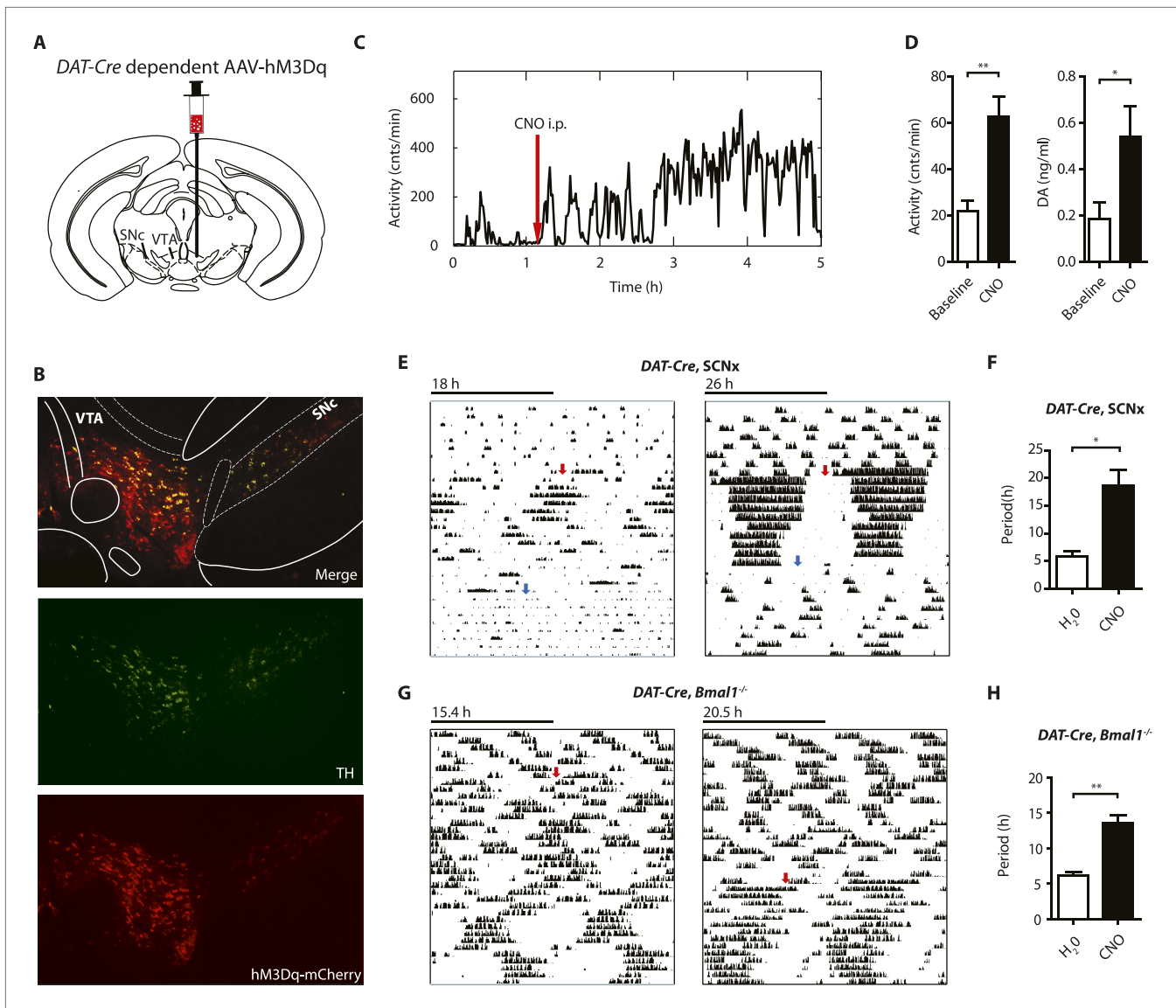


Figure 8. Chemogenetic activation of midbrain DA neurons lengthens ultradian locomotor period. **(A)** AAV-DIO-hM3Dq-mCherry was stereotactically and bilaterally delivered into the VTA/SN region of DAT-Cre transgenic mice as indicated. **(B)** Representative immuno-fluorescent image of the ventral midbrain from a virus-injected and behaviorally responsive mouse showing extensive co-expression of the mCherry fusion-tag in TH-positive cells of the midbrain. **(C)** Locomotor response to CNO (red arrow, 1 mg/kg body weight i.p.) of a representative, AAV-hM3Dq transduced DAT-Cre mouse undergoing microdialysis. **(D)** 20min- binned locomotor activity and extracellular striatal DA content (20 min) of AAV-hM3Dq transduced mice 1 hr prior (Baseline) and 2 hr after CNO injection. Mice were implanted with a striatal microdialysis probe and DA content was measured as in **Figure 6A** (mean $\pm$ SEM; N = 3, *p < 0.05, **p < 0.01, paired t-test). **(E–H)** Representative actograms of AAV-hM3Dq transduced DAT-Cre, SCNx **(E)** and DAT-Cre, Bmal1^{-/-} mice **(G)**. Switch to CNO-containing drinking water (7.5 mg/l) is indicated by red arrow. Blue arrow marks return to regular water (in **E**). Animal activity is plotted modulo according to the period measured during the last 7 days of CNO treatment. Periodogram analysis reveals CNO-dependent period lengthening in both DAT-Cre, SCNx **(F)**, mean $\pm$ SEM; N = 6, $F_{1,5} = 3.68$, *p < 0.05, ANOVA) and DAT-Cre, Bmal1^{-/-} **(H)**, mean $\pm$ SEM; N = 11; $F_{1,10} = 20.48$, **p < 0.0001, ANOVA) mice. VTA, ventral tegmental area; SNc, substantia nigra pars compacta.

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The following figure supplement is available for figure 8:

Figure supplement 1. AAV-h3MDq targeting of DA neurons.

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locomotor behavior in more detail. Under LD conditions, we observed more fragmented daily activity in *Slc6a3*^{-/-} than their wildtype counterparts (**Figure 7A,D**). Upon release into constant darkness (DD), wild-type animals exhibited a daily rhythm with a period slightly shorter than 24 hr as expected for mice (**Bunger et al., 2000**) (**Figure 7A**). While this principal locomotor component was also observed

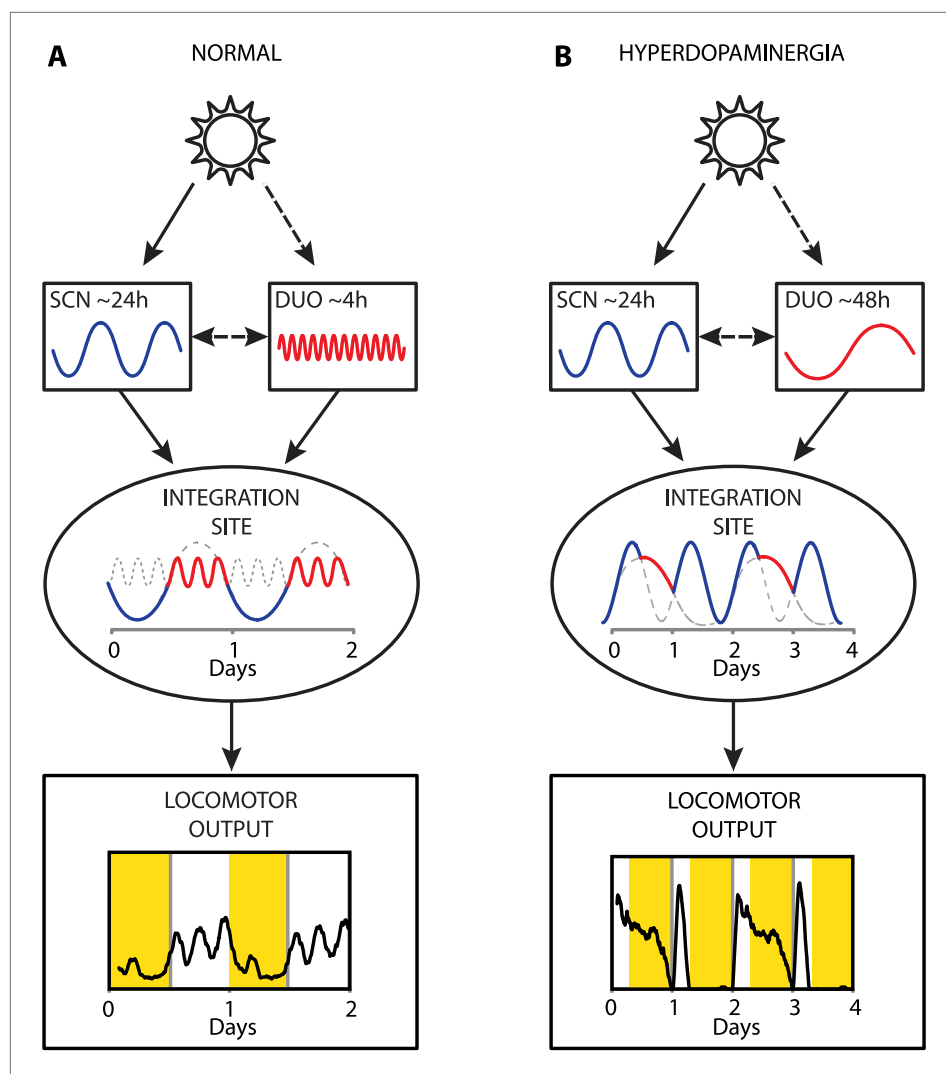


Figure 9. Proposed model of circadian and ultradian oscillator output integration to govern daily locomotor behavior. **(A)** Light input entrains the circadian (SCN) and (indirectly) the ultradian (DUO) oscillators creating a stable phase relationship. Their rhythmic outputs, upon integration at a common downstream effector, generate the daily pattern of locomotor activity. **(B)** Under conditions of high DA tone (e.g., DAT elimination or Meth-treatment), DUO period lengthens, leading to a second, separate activity rhythm. This rhythm either free-runs (see **Figure 7D,G**) or phase locks with the SCN pacemaker by adopting a subharmonic, that is, 48-hr period, as frequently observed upon Meth treatment. Representative output plots show average activity of individual mice computed from 8 days of ambulatory activity **(A)** or 14 days of running wheel activity under Meth treatment **(B)**. DOI: [10.7554/eLife.05105.011](https://doi.org/10.7554/eLife.05105.011)

in *Slc6a3*^{-/-} mice, they repeatedly exhibited an additional activity component with periods longer than 24 hr (**Figure 7D–F**). This component, which was more evident after the first few weeks in DD, extended from the main activity component and lasted for several cycles before disappearing late in the subjective day (**Figure 7D**). Overall, there was no significant difference in the total amount of daily activity even though the temporal pattern of locomotion in these mice is severely altered (**Figure 7C**). The observed dual component activity pattern shows striking similarities to the activity patterns of Meth-treated C57BL/6 mice (**Figure 7G–I**), suggesting that the second rhythmic component is generated by the dopaminergic oscillator.

However, such locomotor activity pattern, with two components oscillating at different frequencies, has also been observed in rats housed under a 22-hr LD cycle and have been attributed to a dissociation of molecular rhythms between the dorsal and ventral SCN (*de la Iglesia et al., 2004*). To rule out that the SCN is similarly affected in *Slc6a3*^{-/-} mice, we sacrificed mice at the peak and trough of the

main activity component when the second rhythm was maximally antiphasic (**Figure 7—figure supplement 1A**). In situ hybridization directed against *Period1* transcripts did not indicate rhythmic desynchrony between or within SCN hemispheres. The riboprobe showed strong, homogenous staining throughout the SCN in the early subjective day, whereas little to no signal was detectable in the early subjective night, suggesting that SCN pacemaker function is unperturbed in *Slc6a3*^{-/-} mice (**Figure 7—figure supplement 1B**).

Together, these findings thus argue that the second rhythmic component of *Slc6a3*^{-/-} mice is indeed a product of the above described dopaminergic oscillator.

Chemogenetic activation of DA neurons lengthens ultradian period

Since striatal and midbrain DA levels vary concordantly with activity rhythms in *Bmal1*^{-/-} mice, and DA neurons of the SN/VTa are by and large the exclusive source of striatal and midbrain DA, these neurons are a likely site of ultradian rhythm regulation, if not generation. To corroborate the importance of these neurons in the oscillator process, we employed a chemogenetic approach based upon DREADD (designer receptors exclusively activated by designer drugs) technology (*Krashes et al., 2011*). We stereotactically delivered the adeno-associated virus AAV-DIO-hM3Dq-mCherry (*Krashes et al., 2011*) into the SN/VTa region of mice that carried an *Slc6a3* promoter driven Cre transgene (DAT-Cre) (**Figure 8A**) (*Turiault et al., 2007*) and that additionally were either BMAL1-deficient (DAT-Cre, *Bmal1*^{-/-}) or received an SCN lesion (DAT-Cre, SCNx). Upon Cre-mediated recombination, virally transduced cells express the stimulatory DREADD hM3Dq, which has been demonstrated to increase neuronal firing frequency upon binding of the compound clozapine-N-oxide (CNO), which is otherwise physiologically inert (*Alexander et al., 2009*). As augmenting firing frequency in DA neurons enhances DA release (*Sulzer, 2011*), and CNO stimulation of successfully transduced DAT-Cre mice evokes vigorous firing of dopamine neurons (*Wang et al., 2013*), CNO is expected to increase DA release. Consistently, i.p.-injection of CNO elevated extracellular DA in the striatum of those mice and led to a prolonged increase in locomotor activity (**Figure 8C,D**), which was absent in vehicle injected animals (**Figure 8—figure supplement 1D**). Responsive mice showed mCherry fusion tag expression selectively in tyrosine hydroxylase (TH) positive cells (**Figure 8B**, **Figure 8—figure supplement 1A**). Cell counting revealed that, $92.9 \pm 5.1\%$ and $87.8 \pm 6.0\%$ (mean $\pm$ SEM, $N = 6$ for both groups) of the midbrain TH⁺ neurons also expressed the mCherry fusion tag in responsive DAT-Cre, SCNx and DAT-Cre, *Bmal1*^{-/-} mice, respectively, confirming effective Cre-mediated hM3Dq expression in midbrain DA neurons. Running wheel activity monitoring of virus-injected mice showed the expected short period locomotor oscillations, however, upon switching to CNO-containing drinking water (red arrows), both, AAV-hM3Dq transduced DAT-Cre, SCNx and DAT-Cre, *Bmal1*^{-/-} mice responded with locomotor period lengthening (**Figure 8E–H**), an effect that was reversed when mice were returned to pure water (**Figure 8G**, blue arrows). As expected, a period lengthening was not observable in AAV-hM3Dq injected DAT-Cre^{0/0}, *Bmal1*^{-/-} mice upon CNO exposure (**Figure 8—figure supplement 1B,C**). These results further corroborate that elevating DA tone, in this case by selective excitation of DA neurons, lengthens ultradian locomotor period and that the oscillator driving ultradian rhythmicity comprises DA neurons of the VTA/SN region.

Discussion

Collectively, our results provide strong evidence that a dopaminergic ultradian oscillator (DUO) driving rhythms of behavioral arousal is continuously operative in the mammalian brain. We propose that under normal conditions, this DUO cycles in harmony with the circadian SCN pacemaker and that the rhythmic information of both the SCN and the DUO are integrated at a common downstream site to create the daily pattern in locomotor activity (**Figure 9A**). However, elevation of DA tone can lead to DUO period lengthening, which either results in DUO free-run (for example, **Figure 7D,G**) or reinstatement of oscillator synchrony albeit at a different harmonic (**Figure 9B**, e.g., 48 hr). The DUO appears as a highly tunable oscillator, able to adopt period lengths from a few hours to multiple days. This is in stark contrast to the circadian timer which cannot adopt periods that are more than a few hours off from 24 hr when its limits of entrainment are tested experimentally (*Aschoff and Pohl, 1978*).

Given that DA is known to stimulate locomotor activity (*Zhou and Palmiter, 1995*), our observation of a cyclical rise in extracellular striatal DA, which is in synchrony with ultradian activity rhythms, argues that DA acts as an output of the DUO. Our finding that manipulations affecting extracellular DA levels alter oscillator period and that extracellular DA tone shows a remarkably high correlation with activity

cycle length, strongly suggests that DA is a period determinant and therefore must be an integral component of the oscillatory mechanism itself. As all period-altering manipulations directly impinge upon DA neuronal physiology, this suggests that either (i) DA neurons are the site of ultradian rhythm generation or (ii) they are a key cog in the oscillatory mechanism. The chemogenetic activation experiments indicate that the relevant DA neuronal population is located in the midbrain as selective activation of DA neurons in this region had a period lengthening effect on the ultradian activity. Future experiments will be aimed at delineating the precise DA population(s) required for the ultradian rhythm generation process and how rhythmic synchrony between neurons is maintained, if the DUO is indeed composed of a population of cellular oscillators.

Our data indicate that the circadian and ultradian locomotor rhythms are normally harmonized (for instance, **Figure 9A**), suggesting that the circadian pacemaker and the DUO interact. Of note, extracellular DA was reported to fluctuate diurnally in the rodent striatum (**Hood et al., 2010**), which was abrogated in *Slc6a3*^{-/-} mice (**Gallardo et al., 2014**). In these studies, only group averaged DA profiles were presented and DA was solely measured in circadian intact mice and rats, thus it is conceivable that any ultradian component (in WT) or infradian component (in *Slc6a3*^{-/-}) escaped detection. Critically, the observation that the DA levels, on average, followed a diurnal pattern with a night-time peak, together with the observation that ultradian locomotor period in female hamsters is longer in the dark vs the daily light phase (**Prendergast et al., 2012**), is consistent with the LD cycle and/or the circadian pacemaker affecting DUO rhythmicity by altering (extracellular) DA. Note however, that dopamine content in whole brain extracts from circadian-intact rats kept under LD showed a strong ultradian variation with no obvious evidence for a diurnal rhythmic component (**Scheving et al., 1968**). Also, microdialysis did not reveal a day:night difference in extracellular DA levels in the striatal NAcc region when measured in DD (**Chung et al., 2014**). This same study reported elevated DA levels and hyperactivity in mice lacking clock gene *Rev-erba*, suggesting that the circadian clock, possibly intrinsic to DA neurons themselves, has a role in DA regulation. Indeed, knockdown of the core circadian clock component *Clock* in DA neurons of the murine VTA, increases electrical firing rate in VTA neurons and enhances locomotor response to novel objects (**Mukherjee et al., 2010**). Interestingly, we did not observe any systematic differences in ultradian locomotor period between SCNx and *Bmal1*^{-/-} mice in constant darkness conditions, regardless of DAT status (**Figures 1, 2**), suggesting that extra-SCN circadian clocks have no role in DUO-mediated ultradian locomotor rhythm generation.

Our data also provide evidence that the postulated MASCO (**Tataroglu et al., 2006**) represents a long-period manifestation of the DUO as a result of methamphetamine's action on the dopamine transporter, blocking dopamine reuptake thereby increasing extracellular DA levels. Interestingly, the dopamine system has been also implicated with another behavioral timing system: the food-entrainable oscillator (FEO). This circadian independent oscillator (**Pitts et al., 2003; Prendergast et al., 2009; Storch and Weitz, 2009**) drives food-anticipatory locomotor activity (FAA) that emerges when food access is restricted to a few hours each day (**Mistlberger, 2011**). D1 (DRD1) and D2 (DRD2) receptor antagonists attenuate FAA additively (**Liu et al., 2012**) while pharmacological DRD2, but not DRD1, activation altered the phase of FAA (**Smit et al., 2013**). Most recently, using knockout mice, it was revealed that DRD1 but not DRD2 is necessary for the appropriate expression of FAA and that rescuing dopamine signaling selectively within the dorsal striatum was sufficient to restore FAA in dopamine-deficient mice (**Gallardo et al., 2014**). Given the links to the dopaminergic system, it will be of interest to investigate whether the DUO has a role in the temporal regulation of FAA.

While these findings argue that food cues engage the dopamine system to alter daily locomotor activity patterns, it is clear that dopamine signaling also affects food intake as mice lacking dopamine are lethargic and do not actively consume food (**Zhou and Palmiter, 1995**). Considering that the DUO is a universal driver of ultradian behavioral rhythms in mammals, the finding that ultradian bouts of running-wheel and feeding activity are co-expressed in the common vole (**van der Veen et al., 2006**) suggests that dopamine can synchronously drive food seeking and general activity, which is in line with the view that dopamine acts as a general promoter of motivated arousal.

Slc6a3^{-/-} mice have been proposed as a model for schizophrenia (**Gainetdinov et al., 2001**) and the DA hypothesis of schizophrenia states that DA elevation is causal to the behavioral symptoms of this psychiatric condition. Intriguingly, circadian (48 hr) or free-running rhythms in locomotor activity reminiscent of the behavioral patterns we detected in *Slc6a3*^{-/-} or Meth-treated mice (**Figures 4F, 7C,F, 9B**) have been observed in schizophrenic subjects (**Wirz-Justice et al., 2001; Wulff et al., 2012**),

suggesting that DUO dysregulation underlies the rest-activity aberrations associated with schizophrenia. Furthermore, actigraphy recordings in schizophrenic patients also revealed that Hal treatment reduces circadian/diurnal locomotor amplitude and leads to the emergence of ultradian activity bouts (Wirz-Justice *et al.*, 1997, 2009), effects we likewise observed in *Slc6a3*^{-/-} mice in response to Hal. Transient DUO period lengthening might equally account for the rest-activity pattern abnormalities observed during manic episodes in bipolar disorder, which has been also associated with altered DA tone (Berk *et al.*, 2007). Bipolar subjects have been reported to show rapid, 48-hr cycling between mania and depression (Gann *et al.*, 1993; Wilk and Hegerl, 2010), one to multiple 48-hr sleep-wake cycles when switching from depression to mania (Wehr *et al.*, 1982), or a long-period ‘free-running’ rhythm of wakefulness (Wehr *et al.*, 1998). Thus schizophrenic and bipolar subjects both appear to exhibit rest-activity cycle aberrations strikingly similar to those observed in *Slc6a3*^{-/-} or Meth-treated mice, suggesting that DUO dysregulation is a common indicator for these psychopathologies and perhaps even a common disease cause.

A switch to sleep-wake cycles with a period much longer than 24 hr have also been observed in subjects that were studied in temporal isolation (Aschoff, 1965). Because other physiological parameters such as urine secretion and core body temperature showed phase-aligned, circadian fluctuations with a period much closer to 24 hr, the subjects were considered internally desynchronized. Notably, affected subjects tend to exhibit high scores of neuroticism (Wever, 1979). It is therefore conceivable that the observed internal desynchronization is also due to a dysregulation of the DUO.

Materials and methods

Animals

Bmal1^{-/-} (Bunger *et al.*, 2000) and *DAT-Cre* (Turiault *et al.*, 2007) mice were on a C57BL/6J genetic background, while *Slc6a3*^{-/-} mice (Giros *et al.*, 1996) were maintained on a mixed C57BL/6JxDBA/2J background (Morice *et al.*, 2004). Animals were housed under LD 12 hr:12 hr unless otherwise stated. *Slc6a3*^{-/-} mice were found to exhibit high attrition rates (~80%) in experiments that involve long-term locomotor activity monitoring. To increase survival, *Slc6a3*^{-/-} mice were first group-housed for 1 week after transfer into the light-tight, ventilated cabinets used for activity monitoring. This was followed by 1 week of individual housing in running wheel cages with the wheels locked before commencing baseline activity recordings. During this adaptation phase and throughout the subsequent experimental period, both *Slc6a3*^{-/-} mice and their wild-type littermates were provided with ad libitum chocolate flavored chow (Supreme Mini-Treats, BioServ, Flemington, NJ) as well as cotton nestlets and ample shredded corrugated card stock. This regimen significantly reduced attrition rates to less than 20% on average. ‘Material and methods’ were performed in accordance with the Canadian Council on Animal Care guidelines and approved by the McGill University Animal Care Committee.

Locomotor activity and core body temperature monitoring

Running wheels: Animals were individually housed in light-controlled cabinets and activity was recorded continuously (ClockLab, Actimetrics, Wilmette, IL). Actograms, displaying binned running wheel revolutions per 6 min (0.1 hr), and the associated Lomb-Scargle periodograms, displaying amplitude, were generated using ClockLab software. **Telemetry:** Animals were individually housed in standard cages placed atop energizer/receiver units (ER-4000, Starr Life Science Corp., Oakmont, PA). 1 week prior to data collection, electromagnetic induction powered telemetry probes (G2 E-mitter, Starr Life Science Corp.) were implanted intraperitoneally. Locomotion, measured in counts per minute, and core body temperature (BT, in °C), was collected in 6-min bins (0.1 hr) using Vitalview software (Starr Life Science Corp.). BT data was exported into Clocklab to generate actogram-style data displays with tick mark height corresponding to temperatures from 34–38°C; for waveform generation, averaging, and 2 hr recursive smoothing, locomotor activity and BT data was exported to Excel (Microsoft, Redmond, WA). Matlab (Mathworks, Natick, MA) was used for ribbon plot generation, and low pass Butterworth filtering (1 hr).

Pharmacology

Stock solutions of (+)-Methamphetamine hydrochloride (100 mg/l, Sigma-Aldrich, St. Louis, MO), D-Amphetamine hemisulfate (100 mg/l, Sigma-Aldrich), Haloperidol (11.25 mg/ml, Sigma-Aldrich) and Clozapine-N-Oxide (15 mg/l, National Institute of Mental Health, Bethesda, MD) were prepared

using distilled water. Methamphetamine solutions were adjusted to pH 7 using sodium hydroxide and haloperidol was dissolved by stirring at 40°C.

Chronic methamphetamine infusion

Mice were continuously infused with methamphetamine (0.6 mg/day in 0.9% saline) for 14 days using subcutaneously implanted osmotic minipumps (Alzet Model 1002, Durect Corp., Cupertino CA). Pumps were fitted with a 65-mm polyvinyl chloride catheter (0.69-mm inner diameter, Plastics One, Roanoke, VA) and backfilled with saline to allow for an approximately 4 day post-surgery recovery prior to drug exposure.

In situ hybridization

In situ hybridization was performed as previously described (*Kraves and Weitz, 2006*). Briefly, following decapitation, brains were removed and quickly frozen at −80°C. Serial coronal hypothalamic brain slices (25 µm) were collected using a cryostat and stored at −80°C until hybridization. Sections were hybridized overnight at 60°C to a digoxigenin-labeled riboprobe targeting the coding regions of mouse *Per1* (nucleotides 579–1478 of the *Per1* mRNA, Genbank, NM_011065.4).

SCN lesions

Electrolytic lesions of the suprachiasmatic nucleus were performed as described (*Storch et al., 2007*). Briefly, an electrode (RNE-300X, Rhodes Medical Instruments, Woodland Hills, CA) was lowered through a hole drilled in the skull at the mid-sagittal sinus according to stereotaxic coordinates (AP −0.25 mm, DV −6.00 mm from Bregma) and a constant current (2 mA, 10 s; D.C. Constant Lesion Maker, Grass Instruments, Quincy, MA) was applied. Only mice with behavioral circadian arrhythmia (in the 20–28-hr range assessed by Lomb-Scargle periodogram analysis) and subsequent post-mortem histological verification using DAPI staining mounting medium (Vectashield, Vector Labs) were included for analysis. This represented approximately 50% of lesioned mice when averaged across all studies.

In vivo microdialysis

1 week prior to sampling, mice were stereotaxically implanted with a guide cannula (C312G/spc 2.5 mm below pedestal, Plastics One), targeting the striatum (AP +1.10 mm, DV +5.5 mm, ML +0.9 mm). 1 day prior to dialysis, mice were transferred to a beam break monitor (VersaMax, Omnitech Electronics, Columbus, OH) and tethered using a dummy probe assembly under constant, dim, red light (<5lux). On the day of sampling, in-house recording probes (*Lupinsky et al., 2010*), were connected to a central swivel (Model 72-0000, Harvard Apparatus, Holliston, MA). Artificial cerebrospinal fluid was delivered via syringe pump (Model 403, CMA Microdialysis, Kista, Sweden) at a flow rate of 1.0 µl/min. This procedure was similarly followed to test the effects of CNO in AAV-transduced *DAT-Cre* mice where intraperitoneal injections of 1 mg/kg CNO were given after approximately 1 hr of baseline sampling. Samples were collected every 20 min for 4 hr and immediately admixed with 1 µl of perchloric acid. DA and DOPAC content in the dialysate were determined by high-performance liquid chromatography with electrochemical detection (HPLC-EC) as described (*Domenger et al., 2012*). Chromatographic peak analysis was conducted using CoulArray software (ESA Inc., Chelmsford, MA). After data collection, brains were removed, sectioned, and stained with hematoxylin to verify probe placement. Locomotor activity data, recorded as the number of beam breaks per minute, were exported into Matlab (Mathworks) for waveform generation, 20-min binning, cosinor modeling, and false discovery rate analysis.

DA/DOPAC content determination in tissue extracts

After decapitation, brains were quickly removed and frozen (−80°C). 320 µm coronal brain slices were obtained by cryosectioning and then microdissected (1- or 2-mm diameter sample corers, Fine Science Tools Inc., Foster City, CA) to obtain tissue of the CPu (2 mm), NAcc (1 mm), and SN/VTA midbrain (2 mm) regions (see *Figure 6G* for punch location). DA/DOPAC was quantified as previously described (*Domenger et al., 2012*). Briefly, individual punches from each region were homogenized in 45 µl perchloric acid (0.25 M) to which 15 µl of a 100 ng/ml solution of 3,4-dihydroxybenzylamine was added, which served as the internal standard. Concentrations were determined by HPLC-EC. After perchloric acid extraction, the protein containing pellets were reconstituted in 0.1 N sodium hydroxide for protein quantification (Pierce BCA Kit, ThermoFisher Scientific, Waltham, MA).

Chemogenetics

Mice were anaesthetized with isoflurane and placed in a stereotaxic apparatus (David Kopf Instruments). Recombinant AAV8-DIO-h3MDq-mCherry (*Krashes et al., 2011*) (titer = 3×10^{12} genomes copies per ml, UNC Vector Core Services, Chapel Hill, NC) was bilaterally injected into the VTA/SN area (coordinates from bregma: AP: -3.44 mm, DV: -4.40 mm, L: ± 0.48 mm) (*Tsai et al., 2009*) through a cannula (33 gauge, Plastics One) at a flow rate of $0.05 \mu\text{l}/\text{min}$ for 10 min ($0.5 \mu\text{l}$ total volume per side) using a syringe pump (Harvard Apparatus). Mice were subsequently maintained in individual housing for at least 2 weeks prior to CNO treatment.

Immunohistochemistry

Immunostaining was performed as previously described (*Chu et al., 2013*) using cryoprotected (30% Sucrose), free-floating coronal sections from fixed brains collected after intra-cardiac perfusion (4% paraformaldehyde) and cut at 40 microns using a cryostat (Leica, Solms, Germany). For fluorescent labeling, sections were incubated overnight with primary antibodies for mCherry (rabbit anti-RFP, 1:1000, Rockland, Limerick, PA) to enhance detection of the mCherry expression and antibodies for tyrosine hydroxylase (mouse anti-TH, 1:1000, EMD Millipore, Etibicoke, Canada). This was followed by 2 hr incubation with secondary antibodies (anti-rabbit Alexa Fluor 567 and anti-mouse Alexa Fluor 647, 1:250, Life Technologies, Carlsbad, CA) after which sections were mounted on superfrost slides (VWR, Radnor, PA), coverslipped with Vectashield mounting medium (Vector Labs, Burlington, Canada) and imaged by fluorescence microscopy (AxioObserver Z1, Zeiss, Jena, Germany). Quantification of co-expression was performed on a single, medial, midbrain section from each behaviorally responsive mouse using the cell counter plugin of ImageJ (National Institute of Health, Bethesda, MD) in order to determine the percentage of all TH-positive cells that also expressed the hM3Dq-mCherry fusion protein ($N = 6$ per genotype).

Statistical analysis

One-way and repeated measures ANOVA, t-tests, and linear regression analyses were performed using Prism 5 (GraphPad, La Jolla, CA). Planned comparisons for the repeated measures were carried out to determine significant period changes between subsequent measurements. Bonferroni correction was used for post-hoc testing of individual group differences.

False discovery rate (FDR) and cosinor determination

To evaluate the probabilistic significance of the least-square fit between the DA trace and the cosinor model that was computed based on the animal's locomotor activity oscillations, a false discovery rate approach was employed (*Storch et al., 2007*). For cosinor computation, we first determined the locomotor period of *Bmal1*^{-/-} mice by Lomb-Scargle periodogram analysis of 20 hr of locomotor recordings following dialysate sampling. The determined period was then used as an input parameter for a least-squares cosinor analysis (*Nelson et al., 1979*) using a custom script and function written for Matlab (<https://github.com/storchlab/Cosinor-FDR.git>). This procedure generated a best-fit (co)sine wave modeling the activity time-series. This model wave was then used to assess the concordance between the extracellular DA fluctuations and locomotor oscillations. To calculate FDR, we randomly permuted the temporal order of the measured DA concentrations 100,000 times, and assessed its fit to the cosinor. The permutation procedure will degrade the fit of any truly rhythmic signal but will have little to no effect on noisy or flat profiles. The probability of false discovery was calculated as the percentage of randomly permuted traces that show an equal or better fit to the cosinor than the measured DA fluctuation.

Butterworth filtering

Low pass filtering (1-hr cut-off) of raw data was conducted using a Butterworth zero-phase filter (*Butterworth, 1930*) in Matlab. This allowed for better visualization of ultradian frequencies in the >1 -hr range, in a manner similar to recursive smoothing but without phase distortion.

Period determination

Ultradian rhythms show variability in amplitude and period. We thus used Lomb-Scargle periodogram analysis (Clocklab) to estimate ultradian period length as this method is relatively tolerant to noisy data and data gaps, which can result from intermittent ultradian rhythm expression (*Press and Rybicki, 1989*). Unless otherwise stated, period length was determined by identifying the highest peak above the significance threshold ($\alpha = 0.01$) in the Lomb-Scargle periodogram. Subsequent

plotting of an actogram at the determined modulus was conducted in each case in order to visually confirm rhythmicity and rule out the false identification of harmonic frequencies or side-lobes due to leakage (Van Dongen et al., 1999).

Continuous wavelet transforms

To visualize and quantify the dynamics of period and amplitude in circadian incompetent mice, continuous wavelet transforms using the Morlet wavelet (Goupillaud et al., 1984) were performed for the 1–12-hr range using custom algorithms written in Matlab (<https://github.com/storchlab/CWT.git>). Locomotor activity data of seven consecutive days per individual SCN-lesioned or *Bmal1*^{-/-} mouse was used. For each spectrogram, a ridge identifying the peak amplitude of the spectrum was generated as described (Leise, 2013) and the associated values were used to calculate the average and standard deviation of the dominant ultradian frequency for each animal.

Amplitude spectral density (ASD)

To determine the prevalence of oscillations in a given period range we calculated the area under the curve of all significantly rhythmic periodicities ($\alpha = 0.01$) in the Lomb-Scargle periodogram, that is, the spectral density. For normalization, the obtained spectral density was divided by the total significant spectral density in the 0–40-hr range and expressed as percentage.

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Ethics

Animal experimentation: All experimental procedures were performed in accordance with the Canadian Council on Animal Care guidelines and approved by the McGill University Animal Care Committee (animal use protocol #2010-5945).

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baseline. Because combined stimulation altered the activation patterns in each of these regions in ways that the single stimuli did not, they were labelled our regions of interest. Given the role they each play in dlPFC and vestibular pathways, the inhibitory function exerted by the dlPFC on vestibular processing likely centres around one or more of these areas.

Research Category and Technology and Methods

Clinical Research: 18. Functional Brain Imaging

Keywords

dlPFC, fMRI, tACS, Vestibular System

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P3.028

INCONSISTENT TMS DOSING IN NON-MOTOR AREAS AS A KEY FACTOR IN INTERINDIVIDUAL VARIABILITY OF TMS/EEG RESPONSES

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Abstract

The field of transcranial magnetic stimulation (TMS) is trending toward increased individualization to improve efficacy and reproducibility in both research and clinical practice. In non-motor regions, one factor driving variability may be the use of motor threshold to set the stimulation intensity.

In this retrospective study, we aimed to assess the impact of e-field strength on TMS/EEG for the inferior parietal lobule (IPL). We performed e-field simulations on individual brain models to estimate e-field strength when TMS was applied at 120% of resting motor threshold (rMT) in 35 older adults (age=71.79±5.9 years, 55.8%female). We also computed TMS-evoked responses at the scalp level as local mean field potentials (LMFP) and at the source level as normalized current densities directly beneath the TMS coil.

Our results revealed that, at the group level, e-field strength was significantly lower in the IPL compared to the M1 region at 120%rMT ($t(1,34)=5.49$, $p<0.001$). Analyses of individual data showed that while most participants were under-dosed (i.e., IPL e-field strength >10% below M1), a few were over-dosed. More importantly, we found positive correlations between e-field strength and local TMS-evoked responses at the source level across multiple early time windows (35–55ms, Spearman's $\rho=0.465$, $p<0.01$). In most time windows, correlations between rMT and e-field strength were lower than those at the source level (35–55ms, Spearman's $\rho=0.299$, $p=0.08$). Notably, we found that e-field strength correlated more robustly with source-level activity than with LMFP (35–55ms, Spearman's $\rho=0.246$, $p=0.07$), suggesting a specific effect of the e-field at the source level.

These findings suggest that dosing based on %rMT obtained from the motor cortex leads to inconsistent stimulation intensities in non-motor areas, potentially contributing to inter-individual variability in TMS-evoked responses. Our results support the use of e-field-based dosing to ensure more effective and standardized cortical stimulation in non-motor regions.

Research Category and Technology and Methods

Basic Research: 10. Transcranial Magnetic Stimulation (TMS)

Keywords

TMS, EEG, E-field modeling

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P3.029

IMPACT OF THETA BURST STIMULATION ON FACE PROCESSING IN AUTISM: INTERIM RESULTS FROM A RANDOMISED CONTROLLED TRIAL

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Abstract

Background: Challenges with face processing are well documented in autism, a condition for which there are no biomedical therapies that target social difficulties. Face processing has been linked to the right temporoparietal junction (rTPJ), and there is both neuroimaging and neurophysiological evidence of atypical rTPJ function in autism. The current study aimed to investigate whether intermittent theta burst stimulation (iTBS) administered to the rTPJ can improve performance on neuropsychological measures of face processing in autism.

Methods: Here we report the interim results from an ongoing randomised controlled trial. Participants ($n = 66$) diagnosed with autism spectrum disorder (aged 14–40 years, $M = 21.32$, $SD = 7.03$; 38 male, 28 female) received four weeks of either active or sham iTBS (600 pulses at 70% resting motor threshold) to the rTPJ (20 sessions), targeted via MRI(T1)-guided neuronavigation. Assessments of face processing (Reading the Mind in the Eyes Test [RMET], Benton Facial Recognition Test [BFRT], and Cambridge Face Memory Test [CFMT]) were conducted before, after, and one month following iTBS. Data were analysed using mixed model analysis of variance.

Results: There was an interaction effect (time x condition) for the BFRT, $F(2, 128) = 5.32$, $p = .006$, $\eta_p^2 = .08$. Follow-up analyses revealed stronger performance in active compared to sham at one-month post iTBS ($p = .016$). There were no interaction effects for the CFMT or RMET. Further analysis, however, revealed significant differences at one-month iTBS on the RMET, $t(61) = 2.11$, $p = .039$, Cohen's $d = 0.53$, with participants who received active stimulation ($M = .73$, $SD = .15$) more accurate than participants who received sham ($M = .65$, $SD = .16$).

Conclusions: These findings suggest that iTBS applied to the rTPJ can improve face processing, which could have clinical implications for biomedical therapeutics in autism.

Research Category and Technology and Methods

Clinical Research: 10. Transcranial Magnetic Stimulation (TMS)

Keywords

autism spectrum disorder, face processing, theta burst stimulation, randomised controlled trial

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P3.030

FREQUENCY-DEPENDENT DEEP BRAIN STIMULATION OF THE LATERAL HYPOTHALAMIC AREA MODULATES AROUSAL LEVEL AND CORE BODY TEMPERATURE IN HEALTHY AND PARKINSONIAN MONKEY

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Abstract

Background: Deep brain stimulation (DBS) has emerged as a promising therapeutic avenue for alleviating motor symptoms in Parkinson's disease (PD). However, non-motor symptoms, such as daytime sleepiness, continue to pose significant challenges in PD management, warranting further investigation. The lateral hypothalamic area (LHA), known for its crucial role in arousal regulation, presents a compelling target for addressing sleep/wake disturbances in PD.

Objective/hypothesis: In this pilot study, we aimed to explore the potential of frequency-dependent DBS within the LHA to modulate arousal levels and core body temperature in a primate model of PD. We hypothesized that high-frequency stimulation would reduce arousal levels and core body temperature, while low-frequency stimulation would enhance arousal and normalize core body temperature, particularly in the context of Parkinsonian pathology.

Methods: We conducted experiments on healthy nonhuman primates, subsequently rendered Parkinsonian through the administration of MPTP. A modified multiple sleep latency test was employed to assess sleepiness levels during both healthy and Parkinsonian states. DBS at varying frequencies was applied within the LHA, and its effects on sleepiness and core body temperature were evaluated.

Results: Our findings demonstrate a frequency-dependent modulation of wakefulness and core body temperature by LHA-DBS. Specifically, high-frequency stimulation elicited a reduction in arousal levels and core body temperature in healthy states, whereas low-frequency stimulation led to increased arousal levels and normalized core body temperature in Parkinsonian conditions characterized by daytime sleepiness.

Conclusion: The present study highlights the potential of frequency-dependent DBS within the LHA as a novel therapeutic approach for addressing non-motor symptoms, such as daytime sleepiness, in PD. Our findings offer valuable insights into the intricate mechanisms underlying arousal regulation and suggest promising avenues for future research aimed at refining DBS interventions for improved PD management.

Research Category and Technology and Methods

Translational Research: 1. Deep Brain Stimulation (DBS)

Keywords

Parkinson's disease, Lateral hypothalamic area, Deep brain stimulation, Excessive daytime sleepiness

<http://dx.doi.org/10.1016/j.brs.2024.12.944>

P3.031**SUBTHALAMIC LOCAL FIELD POTENTIAL DYNAMICS DURING MOTOR CORTEX AND BASAL GANGLIA TRANSCRANIAL ULTRASOUND STIMULATION**

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Abstract

Low-intensity transcranial ultrasound stimulation (TUS) is a promising non-invasive neuromodulation method. Despite significant advancements in understanding the effects of TUS on cortical areas in animal models and healthy individuals, its impact on deep brain structures, especially in patient populations, remains largely unexplored. Herein, we examined the effects of TUS on the globus pallidus interna (GPi) and motor cortex (M1) in Parkinson's disease (PD) patients by recording local field potentials (LFPs) directly from the subthalamic nucleus (STN).

Seventeen PD patients with bilateral STN Percept PC deep brain stimulation (DBS) systems participated in this sham-controlled study. We applied theta burst (5Hz) TUS (tbTUS) for 2 minutes to each hemisphere targeting M1, GPi, and occipital cortex in separate sessions. LFPs were recorded simultaneously before, during, and at 10, 30, and 45 minutes after the sonications. During the sham condition, the procedure was performed with the stimulation intensity set to 0 watts.

Patients reported no adverse events related to TUS. Compared to the sham condition, M1-tbTUS significantly increased theta power and suppressed beta power, whereas GPi-tbTUS increased beta power. These effects persisted for at least 45 minutes. In contrast, occipital cortex-tbTUS (active

sham) did not differ significantly from the passive sham condition. Movement (finger tapping task) significantly amplified the effects of M1-tbTUS on the alpha band.

These results provide direct evidence of target engagement and specificity of TUS in cortical and deep brain structures in humans and offer promising insights into its potential as a safe, non-invasive brain stimulation technology for treating neurological disorders.

Research Category and Technology and Methods

Translational Research: 6. Pulsed Ultrasound (pUS)

Keywords

focused ultrasound neuromodulation, local field potentials, Parkinson's Disease, deep brain stimulation

<http://dx.doi.org/10.1016/j.brs.2024.12.945>

P3.032**EXCESSIVE PALLIDAL BETA-BAND ACTIVITY & FUNCTIONAL CONNECTIVITY: A NOVEL INTRACRANIAL BIOMARKER OF STATUS DYSTONICUS**

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Abstract

Objective:

Characterize novel neural correlates of status dystonicus (SD) and assess their relation to clinical severity.

Background:

SD is an emergency with severe episodes of dystonia, necessitating urgent hospital admission. Deep brain stimulation (DBS) of the globus pallidus interna (GPi) is a treatment for refractory SD. Intracranial neural correlates to SD-states and corresponding clinical severity are unknown.

Methods:

Nine patients with SD (Hospital for Sick Children, Canada) were implanted with sensing-capable Medtronic Percept™ GPi DBS (age: 7.8±3.6). Local Field Potentials (LFPs) were recorded at multiple time points during SD and after recovery in non-SD states longitudinally (6-36 months; range: 11-1155 days; average: 319±358 days) and Power Spectral Densities (PSDs) calculated (Welch-method). Analysis of PSD periodic and aperiodic components was performed using fitting-oscillations/one-over-f methods. Band-limited power (Theta: 3-7Hz; Alpha: 7-12.5Hz, Beta: 12.5-30Hz, Gamma: 30-60Hz) was calculated. Intra-pallidal functional connectivity in SD and non-SD was computed using magnitude squared coherence (MSC) between outer (contact 3-referenced-to-2) and inner (1-to-0) GPi. Mixed effects models (MEMs) assessed relations between LFP metrics and clinical scales, including Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) and Pediatric Quality of Life Score (PedsQL).

Results:

Across all patient recordings at optimal contact points, the peak power of the periodic component of the LFP in the beta-band ($p=0.01$) and band-limited beta-band power ($p<0.001$) increased in SD compared to non-SD. GPi beta-band MSC ($p<0.001$) increased in SD (0.24 ± 0.10) from non-SD (0.16 ± 0.08). MEMs controlling for random effects of patient and time determined significant correlation ($R^2=0.80$) between decreased PedsQL and increased beta power ($p=0.004$; intercept $p=0.007$). Results were beta-band specific with no significant associations with theta ($p=0.793$) or alpha-band power ($p=0.877$). Similar results were seen for PedsQL motor-subscores but not BFMDRS.

Conclusions:

Excessive pallidal beta-band activity and functional connectivity are newly described biomarkers of SD, correlating with clinical severity.

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Abstract

Typically, neuropsychological studies of sex offenders have grouped together different types of individuals and different types of measures. This is why results have tended to be nonspecific and divergent across studies. Against this background, the authors undertook a review of the literature regarding the neuropsychology of sex offenders, taking into account subgroups based on criminological theories. They also conducted a meta-analysis of the data to demonstrate the cognitive heterogeneity of sex offenders statistically. Their main objective was to test the hypothesis to the effect that the neuropsychological deficits of sex offenders are not broad and generalized compared with specific subgroups of participants based on specific measures. In all, 23 neuropsychological studies reporting data on 1,756 participants were taken into consideration. As expected, a highly significant, broad, and heterogeneous overall effect size was found. Taking subgroups of participants and specific cognitive measures into account significantly improved homogeneity. Sex offenders against children tended to obtain lower scores than did sex offenders against adults on higher order executive functions, whereas sex offenders against adults tended to obtain results similar to those of non-sex offenders, with lower scores in verbal fluency and inhibition. However, it is concluded that neuropsychological data on sex offenders are still too scarce to confirm these trends or to test more precise hypotheses. For greater clinical relevance, future neuropsychological studies should consider specific subgroups of participants and measures to verify the presence of different cognitive profiles.

Keywords

neuropsychology, cognition, sexual deviance, sex offenders, pedophiles

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The etiological and risk factors in pedophilia and sexual deviance are notoriously complex, with intricate biopsychosocial roots (e.g., Seto, 2008a, 2008b). From a biological perspective, neurodevelopmental abnormalities are commonly suspected to be involved in pedophilia although the evidence for this is indirect and causality is unclear (e.g., left-handedness, different fraternal birth order, second-to-fourth-finger-length ratio, childhood traumatic brain injuries; Blanchard et al., 2003; Cantor, Klassen, et al., 2005; Quinsey, 2003; Rahman & Symeonides, 2008). Neuropsychological studies have generally found sex offenders to present significant cognitive impairments. However, the research has typically focused on heterogeneous groups of participants and batteries of different measures, which might explain the nonspecific and divergent results obtained (for reviews, see Blanchard, Cantor, & Robichaud, 2006, and Joyal, Black, & Dassylva, 2007). Consequently, a fundamental question remains unanswered concerning cognitive impairments in sex offenders: Are they specific or generalized? As pointed out by Blanchard et al. (2006), older neuropsychological studies as a whole have strongly suggested the presence of general cognitive impairments in sex offenders detected by virtually all measures. However, more specific deficits might be identified if subtypes of sex offenders and subtypes of cognitive measures were considered (Joyal et al., 2007). This type of results would illustrate the usefulness of neuropsychological evaluation with sexual offenders, which is still underused in the field. Against this background and in light of the recent interest in the cognitive evaluation of sex offenders (Cohen, Nesci, Steinfeld, Haeri, & Galyner, 2010; Eastvold, Suchy, & Strassberg, 2011; Kruger & Schiffer, 2011; Schiffer & Vonlaufen, 2011; Suchy, Whittaker, Strassberg, & Eastvold, 2009), we conducted a comprehensive review of the relevant literature. Second, we performed a meta-analysis of the data to demonstrate the cognitive heterogeneity of sex offenders statistically and the ineffectiveness of grouping these offenders together for neuropsychological evaluation. A meta-analysis would also help estimating the relative effects reported in previous studies and identifying potentially important moderators. Third, we sought to determine whether subgroups of sex offenders would present more specific cognitive profiles when distinct measures were used.

Neuropsychological research has recently begun distinguishing subgroups of offenders and different cognitive profiles have tended to emerge, for instance, between pedophilic and nonpedophilic child molesters (Eastvold et al., 2011; Schiffer & Vonlaufen, 2011; Suchy et al., 2009). The use of measures that target more specific dimensions, such as impulsivity versus reasoning, instead of broad cognitive categories such as "executive functions" seems fruitful. If subtypes of sex offenders can be associated with particular cognitive profiles, then neuropsychological evaluation could further our understanding and improve prevention of sexual offending. Inversely, if all sex offenders present similar profiles of broad, generalized cognitive impairments, neuropsychological examination would have limited utility.

The Neuropsychology of Sex Offenders

Sex offenders are clearly seen as a heterogeneous group in criminology and psychology. Several typologies have been proposed to distinguish subgroups

(e.g., Marshall, Laws, & Barbaree, 1990; Prentky, Knight, Rosenberg, & Lee, 1989). Surprisingly, neuropsychological studies have tended to ignore these typologies and to group subtypes of sex offenders and/or subtypes of cognitive measures (merging together pedophilic child molesters and rapists of adults, for instance, or using composite scores of neuropsychological batteries; e.g., Flor-Henry, 1987; Langevin & Curnoe, 2008a; Langevin, Wortzman, Wright, & Handy, 1988; Spinella, White, Frank, & Schiraldi, 2006; Young, Justice, & Edberg, 2010). This approach has yielded the classic neurobiological hypothesis of sexual deviance, which attributes a prominent role to fronto-temporal anomalies, especially in the left hemisphere (e.g., Flor-Henry, 1987; Gillespie & McKenzie, 2000; Lang, 1993; O'Carroll, 1989). These fronto-temporal anomalies and their neuropsychological manifestations, however, are neither specific nor characteristic of sex offenders, as they are associated with a wide array of conditions from conduct disorders (e.g., Moffitt & Silva, 1988) to schizophrenia (Heinrichs & Zakzanis, 1998). More recently, the so-called executive functions have been the main focus of neuropsychological studies of sex offenders (Cohen et al., 2010; Eastvold et al., 2011; Schiffer & Vonlaufen, 2011; Stone & Thompson, 2001). However, the term "executive functions" refers to a broad range of capacities, which might explain in part the lack of convergence and specificity across studies. This is why both specific subgroups of participants and more targeted measures of cognition should be considered in the aim of determining the existence of particular neuropsychological profiles among sex offenders. Based on criminological and psychological theories (e.g., Knight & Prentky, 1990; Marshall et al., 1990; for a review of the theories see Ward, Polaschek, & Beech, 2006; for a review of the discriminative factors see Seto & Lalumière, 2010) and existing neuropsychological studies of sex offenders, at least three fundamental moderating factors can be used to distinguish subgroups of participants and measures: (a) age of victim (prepubescent vs. adult/peer); (b) type of neuropsychological assessment; and (c) type of comparison group.

Moderator 1: Age of Victim (Prepubescent vs. Adult/Peer)

Neuropsychological studies have commonly grouped child molesters with prepubescent victims together with rapists (adult/peer victims) in their analyses. Despite the little direct evidence presently available to this effect, these two subgroups should present distinct cognitive profiles. First, a narrative review of older studies underlined that child molesters seemed to exhibit more diverse and more severe cognitive dysfunctions than did sex offenders against adults/peers (Joyal et al., 2007; see also Langevin & Curnoe, 2008a). Second, as a group, child molesters have a lower mean IQ than do rapists of adults (Cantor, Blanchard, Robichaud, & Christensen, 2005a), and a significant correlation exists between mean IQ of child molesters and age cutoff for child victims (Cantor, Blanchard, Christensen, Dickey, & Klassen, 2004). Although IQ levels are not necessarily associated with status of cognitive functioning, we might hypothesize that sex offenders against children on average show more neuropsychological deficits than do sex offenders against adults/peers.

Another important aspect to consider in the neuropsychology of sex offenders is the distinction between sexual deviance (i.e., atypical sexual interests) and antisociality

(e.g., impulsivity, substance abuse, antisocial environment). These are two fundamental factors in classic models of sexual offending (e.g., Hall & Hirschman, 1991; Knight & Prentky, 1990). The two explain significant and distinct, albeit overlapping, proportions of variance in sexual offending and reoffending (McCann & Lussier, 2008). Each factor might also be related to distinct neuropsychological profiles. Sexual deviance such as sexual attraction to children is traditionally linked with asocial traits, including isolation, poor interpersonal and courtship skills, low self-esteem, feelings of inadequacy, lack of assertiveness, fear of rejection, and lack of sexual knowledge (e.g., Davis & Leitenberg, 1987; for reviews, see Seto, 2008a, 2008b). In psychiatry, asociality is clearly predictive of more severe cognitive impairments affecting in particular the higher order executive functions (e.g., reasoning, deduction, cognitive flexibility, working memory; Gilotty, Kenworthy, Sirian, Black, & Wagner, 2002; Green, Olivier, Crawley, Penn, and Silverstein, 2005; Schonfeld, Paley, Frankel, & O'Connor, 2006). The presence of antisocial behaviors is associated with less cognitive impairment among persons with a severe mental illness (Joyal, Hallé, Lapierre, & Hodgins, 2003).

Given that a previous meta-analysis confirmed that child molesters as a group present weaker social skills for interacting with the opposite sex than do sex offenders against adults (Dreznick, 2003), we might hypothesize that they present more cognitive impairments overall than do sex offenders against adults because cognitive impairment and social skill deficits are related. In this regard, unpublished data suggest that among sex offenders, those who victimize prepubescent children are more socially reclusive, less likely to have lived independently and to have been married, less intelligent, and more likely to present cognitive deficits and psychopathology (King, 2010).

Moderator 2: Type of Comparison Group

Given the high prevalence of psychological comorbid conditions and criminological histories reported among sex offenders, it comes as no surprise that they obtain significantly poorer neuropsychological results compared with the general population (Blanchard et al., 2006). However, other comparison groups, such as antisocial non-sex offenders, should also be considered given the key role of antisociality in sexual offending (Seto & Lalumière, 2010). Sex offenders of the antisocial type are opportunistic and self-centered, act without premeditation, often present an associated substance abuse problem, and are at lower risk of recidivism for sexual offending than for non-sexual offending (McCann & Lussier, 2008). Consequently, this type of offender might simply present a neuropsychological profile similar to that of general offenders. This profile is clearly associated with impulsivity (e.g., lack of inhibition, high risk-taking tendencies, low consideration for consequences, weak sustained attention, poor operant conditioning) and verbal processing impairments (e.g., Moffitt & Henry, 1989; Moffitt & Silva, 1988; White et al., 1994; for a meta-analysis see Ogilvie, Stewart, Chan, & Shum, 2011). Working-memory deficits and other higher order executive dysfunctions have also been reported although these have been observed

more specifically in chronically violent persons (e.g., Séguin, Nagin, Assaad, & Tremblay, 2004). In this regard, antisocial and psychopathic juvenile delinquents demonstrate good higher order executive functions when they cooperate, especially respecting capacities assessed with the Wisconsin Card Sorting Task (WCST; Moffitt & Henry, 1989; Moffitt & Silva, 1988; Roussy & Toupin, 2000).

Moderator 3: Type of Neuropsychological Assessment

Pioneer neuropsychological studies of sex offenders tended to report global composite scores from neuropsychological test batteries (e.g., Graber, Hartmann, Coffman, Huey, & Golden, 1982; Hucker et al., 1986; Langevin, Ben-Aron, Wright, Marcheses, & Handy, 1988; Langevin, Curnoe, & Bain, 2000; Langevin, Glancy, Curnoe, & Bain, 1999; Langevin, Lang, Wortzman, Frenzel, & Wright, 1989; Langevin, Wortzman, Dickey, Wright, & Handy, 1988; Langevin, Wortzman, Wright, & Handy, 1989; Plante, Manuel, and Bryant, 1996; Scott, Cole, McKay, Golden, & Liggett, 1984). These generated nonspecific and divergent results (Blanchard et al., 2006). To evaluate specific neuropsychological hypotheses concerning subgroups of sex offenders, individual validated and specialized measures should be used (for a compendium of neuropsychological assessments, see Lezak, Howieson, Bigler, & Tranel, 2012).

Measures of executive functions are of particular interest in that an association has been suggested between sexual deviance and dysexecutive symptoms (Eastvold et al., 2011; Schiffer & Vonlaufen, 2011). However, the distinction between lower order executive functions (e.g., behavioral inhibition, control of interference, selective attention) and higher order ones (e.g., reasoning, deduction, planning, cognitive flexibility) has rarely been made. Such a distinction would help refine hypotheses. For instance, classic tests of executive functions such as the Stroop task (Stroop, 1935) and the Trail-Making B task (Army Individual Test Battery, 1944) are more sensitive to impulsivity and poor control of interference than other measures of executive functions. Other classic tests of executive functions such as the Category Test (Reitan, 1955), the Wisconsin Card Sorting Task (WCST; Berg, 1948), and Raven's Matrices (Raven, 1982) measure higher order executive functions. Although these traditional tests are not as specific as more recent measures, they should at least be considered separately. In addition, measures of cognitive functions not considered to be "executive" should also be used, including verbal-learning and memory tasks such as the Logical Memory Test (Wechsler, 1987) and verbal-fluency tasks, such as the Controlled Oral Word Association Test (Benton & Hamsher, 1989). In short, to test specific hypotheses, individual measures must be used.

In light of the above, we could expect a double dissociation to emerge between measures of lower and higher order executive functions, on one hand, and asocial and antisocial sex offenders, on the other. Given that antisociality is more closely related to the sexual victimization of peers/adults than to that of children (McCann & Lussier, 2008; Seto & Lalumière, 2010) and that the opposite is true for asociality, it is reasonable to posit that the two groups differ in terms of their cognitive profiles.

In sum, to be clinically relevant in the field of sexual deviance, neuropsychological studies should consider more homogeneous subgroups of participants and individual cognitive measures. Demonstrating that subgroups of sex offenders present different cognitive deficits would help improve our understanding of sex offenders and their treatment, as well as the prevention of sex offending. It could in time contribute also to individual neuropsychological profiling and recidivism risk assessment.

The main goal of this study, then, was to perform a meta-analysis of existing neuropsychological studies of sex offenders and to test the capacity of three fundamental moderators to generate more cognitively homogeneous subgroups. The purpose of the meta-analysis was to calculate and compare effect sizes of different subgroups of offenders with different types of cognitive measures. More specifically, the following hypotheses were tested:

Hypotheses 1: The overall effect size of neuropsychological differences (all types) between sex offenders (all types) and the general population would be significantly heterogeneous.

Hypotheses 2: Each moderating factor (age of victim; type of cognitive domain; and type of comparison group) would significantly improve the homogeneity of the data.

Hypotheses 3: Sex offenders against children would be more cognitively impaired than sex offenders against adults.

Hypotheses 4: Sex offenders against adults would score lower than sex offenders against children on tasks that are sensitive to antisociality.

Hypotheses 5: Sex offenders against adults and non-sex offenders would present comparable neuropsychological profiles.

Method

Data Search

An extensive literature search was performed in various computerized databases (Scopus, Web of Science, Google scholar, Dissertations and Theses, Medline, and PsycInfo) on combinations of the following keywords: pedophilia, pedophiles, sex offenders, sexual deviance, child molesters, rapists, paraphilia, cognition, neuropsychology, neurocognition, and executive functions. Both published and unpublished data sets were considered (e.g., dissertations, theses, proceedings, and personal communications). The reference lists of all pertinent papers were inspected as well, as were all studies that referred to these papers and all related papers identified by the search engines. All studies published prior to June 2011 were taken into account. To be included in the meta-analysis, studies had to meet three conditions: (a) contain at least one individual neuropsychological measure (as opposed to general indexes from neuropsychological batteries; reports limited to IQ were excluded as an excellent meta-analysis focused exclusively on the IQ of sex offenders already existed, i.e.,

Cantor et al., 2005a); (b) provide minimal statistical information to calculate effect sizes (e.g., N , mean, and standard deviation for direct calculations or other type of information such as exact probability levels or frequency distributions for estimations using formulas proposed by Lipsey & Wilson, 2001); and (c) include a comparison group (either a control group, another experimental group, or both).

Statistical Analyses

Variable coding was carried out following the guidelines and forms proposed by Lipsey and Wilson (2001). The effect sizes of the mean differences between sex offenders and controls were calculated for each neuropsychological measure using the Comprehensive Meta-Analysis Software, version 2 (Biostat Inc., Englewood, NJ, USA). Cohen's d (standardized mean difference using pooled standard deviations) was used to generate an overall (average) effect size across all studies along with 95% confidence intervals. To increase stability, a measure had to have been used in at least four studies to be included in the meta-analysis. The overall (mean) effect size was based on all types of sex offenders and all neuropsychological variables, and effect sizes of .20, .50, and .80 were used as thresholds to define small, medium, and large effects, respectively (Cohen, 1988). Each study could contribute only one effect size per variable category, and all effect sizes were independent within a category. Effect sizes obtained in larger studies were not given more weight than those obtained in smaller studies (e.g., with the inverse-variance method; Hedges & Olkin, 1985; Higgins & Green, 2008; Lipsey & Wilson, 2001) as the latter were pioneer reports with more methodological limitations (e.g., participant overlap, file-based collection of clinical data, reporting of composite scores from neuropsychological batteries, unmatched comparison groups; e.g., Hucker et al., 1986; Hucker, Langevin, Dickey, et al., 1988; Langevin, Ben-Aron, et al., 1988; Langevin et al., 1985; Langevin, Lang, et al., 1989; Langevin, Wortzman, et al., 1988, 1989; for critical reviews see Blanchard et al., 2006; Joyal et al., 2007). Therefore, results were entered in straight-forward fashion.

The meta-analysis was based on random effects, which constitutes a more conservative model, as several factors that could not be controlled owing to the small number of available studies were expected to intervene within the effect sizes. It is assumed under this model that effect sizes can differ because characteristics vary from one study to another, whereas in a fixed-effects model, it is assumed that all studies are derived from a common population and that the only source of variation across studies is random error, which was not the case here (Lipsey & Wilson, 2001; Thompson & Higgins, 2002). Possible intervening factors include validity of diagnosis, presence of matched or unmatched control group, nature of comparison group (e.g., violent non-sexual vs. nonviolent property offenders; general population), distinction between preferential and situational type of sex offender against children (e.g., exclusive pedophilia), criminal history (e.g., various types of crimes vs. specialized, only sex crimes), validity of neuropsychological tasks, distinction between measures of cognitive

functions (e.g., verbal memory) and executive functions (e.g., working memory), and distinction between lower order (e.g., impulsivity) and higher order (e.g., reasoning) executive functions. Because the number of meta-analysis moderators should be determined a priori, based on theoretical grounds and having a sufficient number of studies (Higgins & Green, 2008; Lipsey & Wilson, 2001), we considered the following three moderators: (a) age of victim (sex offenders against children vs. sex offenders against adults), (b) type of cognitive domain and neuropsychological measure involved and (c) type of comparison group (general population vs. non-sex offenders).

Regarding the first hypothesis, a Q-test of heterogeneity was conducted to determine whether the observed effect sizes across existing studies (all groups of sex offenders and different types of cognitive measures) resulted from sampling the same population of effect sizes. A significant Q-value indicates that variance in effect sizes across studies is due to factors other than sampling error, suggesting that systematic differences across the studies might be causing meaningful differences in the effects (Hedges & Olkin, 1985; Hunter & Schmidt, 2004; Lipsey & Wilson, 2001). For the purposes of our study, variability in the distribution of the effect sizes used to compute the overall effect size was expected to exceed that of sampling error alone, and the overall effect size was *not* expected to meet the requirement of the homogeneity test. When statistically significant, the Q-test of heterogeneity justifies the quest for moderating factors. Consequently, additional Q-tests of homogeneity were performed to determine whether moderating factors accounted for a significant portion of the overall heterogeneity. Between-group differences were assessed with an ANOVA analog based on the Q-test, which groups effect sizes into mutually exclusive categories on the basis of an independent variable and represents a measure of the magnitude of the effect size difference between groups (Lipsey & Wilson, 2001). When the number of effect sizes was insufficient to conduct an ANOVA analog (i.e., fewer than 10 studies; Higgins & Green, 2008), we evaluated the statistical significance of the difference between groups by excluding zero in the confidence intervals (Seto & Lalumiere, 2010).

Results

The bibliographical search generated 141 references, including 113 different published or unpublished neuropsychological studies involving sex offenders as participants (see references with an asterisk in the reference list). However, approximately half of the neuropsychological studies ($N = 63$) focused exclusively on IQ and were therefore excluded (see Cantor et al., 2005a, for a meta-analysis of IQ reports regarding sex offenders). Among the studies that reported cognitive evaluations other than IQ measures, some were clinical reports or small research projects involving few participants and no comparison group (Bowden, 1989; Burns & Swerdlow, 2003; Cassens, Ford, Lothstein, & Gallenstein, 1988; Graber et al., 1982; Mendez, Chow, Ringman, Twitchell, & Hinkin, 2000; Pflugradt & Allen, 2010; Tost et al., 2004; Walhberg et al., 2003). Other studies reported only global indexes of neurological integrity from neuropsychological batteries (e.g., with the Reitan or Luria-Nebraska batteries; Hucker et al., 1986; Hucker, Langevin, & Bain, 1988; Hucker, Langevin, Dickey, et al., 1988;

Plante et al., 1996; Scott et al., 1984; Yeudall, 1977), scaled or standardized scores (e.g., *T*-scores or *z* scores; Flor-Henry, 1987; Knox-Jones, 1995; Martin, 1999; Young et al., 2010), or composite scores (Kelly, Richardson, Hunter, & Knapp, 2002; Langevin & Curnoe, 2008a; Simpson Tate, Ferry, Hodgkinson, & Blaszczyński, 2001). In these cases, attempts were made to contact the principal author to obtain additional information, which we managed to do for three data sets (our thanks to Lisa Cohen, Angela Eastvold, and Yana Suchy for their kind replies). Two German studies had to be excluded (Schiffer, Krueger, et al., 2008; Schiffer, Paul, et al., 2008) because participants overlapped with a third report that we did include (Kruger & Schiffer, 2011; our thanks to Boris Schiffer and Tillman Kruger for confirming the information). In a few rare cases, different reports used the same control group. These were included but with one common control group (e.g., Langevin, Lang, et al., 1989; Langevin, Wortzman, et al., 1988, 1989). Finally, as certain neuropsychological tasks were used in fewer than four studies, they could not be compared (Cantor et al., 2004; Fazel, O'Donnell, Hope, Gulati, & Jacoby, 2007; Hambridge, 1994; Spinella et al. 2006; Valliant Gauthier, Pottier, & Kosmyna, 2000).

In the end, 23 neuropsychological studies reporting data on 1,756 different participants were included in the meta-analysis (see Table 1 and references with three asterisks in the reference list). Of these participants, 1,063 were sex offenders (of whom 530 victimized children), 375 were non-sex offenders (of whom 78 were violent), and 318 were recruited in the general population (no criminal record). Ten neuropsychological variables were reported (raw data) with sufficient consistency (in at least four studies) to be coded for the meta-analysis: The Stroop interference condition (time; cognitive inhibition), the trail-making B task (time; speed processing and switching), the Wisconsin Card Sorting Task (categories, perseveration, and correct responses; reasoning and cognitive flexibility), the Halstead-Reitan Category Task (number of correct responses; reasoning), Raven's Standard Progressive Matrices (total score; reasoning and fluid intelligence), the Control Oral Word Association Test (COWAT; number of correct responses; verbal fluency), the logical memory subtest (delayed recall; memory), and the visual reproduction subtest (delayed recall; memory) of the Wechsler Memory Scale (see Table 1). A total of 147 effect sizes were calculated, of which all but eight were based on means and standard deviations.

Overall cognitive performance of sex offenders versus general population. Fourteen comparisons were available between sex offenders and members of the general population with all cognitive measures combined (Table 2). A highly significant overall effect size was noted between the groups when all neuropsychological tasks were combined ($d = 0.592$, $SD = 0.024$, 95% confidence interval: [0.292, 0.893], z score = 3.86; $p < .0001$). As expected, however, these effect sizes were not homogeneous across studies ($Q = 43.58$, $df = 13$; $p < .0001$), confirming the need to include moderators. The first moderator entered in the analysis was age of victim. When sex offenders against children (12 years old or younger) were considered separately from sex offenders against adults, the level of heterogeneity diminished considerably though it did remain significant ($Q_{within} = 22.8$, $df = 12$, $p = .03$). This result suggested that homogeneity increased

Table 1. Studies and Overall Effect Sizes Included in the Meta-Analysis (Statistical Significance in Bold; Positive Values Indicate Better Performance From the Comparison Group).

Study	Comparison (N)	Measure	EF	Z	Q
Abracen (1991)	SOC (12) vs. Ctrl (13)	All	0.92*	2.2	0.05
		Raven	0.98*	2.3	
		Trail-B	0.85*	2.0	
Cohen et al. (2002)	SOC (22) vs. Ctrl (24)	All	0.02	0.07	2.59
		Trail B	-0.21	-0.7	
		WCST-Cat	0.0	0.0	
		WCST-Cor	0.28	1.0	
		WCST-Per	-0.2	-0.6	
		COWAT	0.01	0.9	
		Stroop	0.25	0.8	
Cohen et al. (2010)	SOC (22-50) vs. Ctrl (20-87)	All	0.15	0.6	10.97*
		Trail B	-0.21	-0.7	
		WCST-Cat	0.0	0.0	
		WCST-Cor	0.28	1.0	
		WCST-Per	-0.2	-0.6	
		COWAT	0.01	0.9	
		Stroop	0.25	0.8	
Dolan et al. (2002)	SO (20) vs. HO (27)	All	0.31	1.0	5.02
		Trail B	-0.17	-0.57	
		WCST Per	0.54*	1.80	
		COWAT	0.13	0.49	
		Logical memory	0.38	1.26	
		Visual memory	0.67*	2.20	
Eastvold et al. (2011)	Pedo (30) & CM (30) vs. NSO (29)	All	0.20	1.1	14.43**
	SOC vs. NSO	Trail B	-0.34	-1.31	
		COWAT	0.17	0.6	5
		Stroop	0.56*	2.1	
	Pedo vs. NSO	Trail B	-0.21	-0.79	
		COWAT	0.25	0.95	
		Stroop	0.86**	3.2	
Gillepsie and McKenzie (2000)	SO (8) vs. NSO (8)	All	0.32	0.6	2.70
		Trail B	-0.26	-0.45	
		COWAT	0.89*	1.7	

(continued)

Table 1. (continued)

Study	Comparison (N)	Measure	EF	Z	Q
Joyal et al. (2007)	SOC (12) & SO (8) vs. Ctrl (13-118) SOC vs. Ctrl	Stroop	0.11	0.22	49.39***
		Raven	0.5	1.02	
		All	0.64**	2.3	
		Trail B	0.09	0.23	5.2 -0.15
		WCST Cat	0.05	0.17	
		WCST Per	-0.29	-0.89	
		COWAT	1.98***	4.8	
		Stroop		1.67***	
		SO vs. Ctrl	Trail B	-0.07	
		WCST Cat	0.11	0.28	
		WCST Per	0.03	0.07	
		COWAT	2.02***	4.39	
Kruger and Schiffer (2011)	Pedo (20) vs. Ctrl (28)	Stroop		0.68*	1.85 0.17
		All	0.42	1.4	
		WCST Cor	0.51*	1.72	
Langevin et al. (1985)	Pedo (32) vs. Ctrl (54)	WCST Per	0.34	1.14	I.D
		Raven	0.58**	I.D	
Langevin et al. (1988)	Incest (88) vs. NSO (14)	Trail B	0.76**	I.D	
Langevin et al. (1989a)	Pedo (114) vs. NSO (31)	Trail B	0.48	I.D	
Langevin et al. (1989b)	Exhibitionists (13) vs. NSO (14)	Trail B	0.50	I.D	
Miller (1998)	SO (50) vs. NSO (50)	All	0.28	1.4	2.34
O'Carroll (1989)	SO (11) vs. Ctrl (11)	WCST Cat	0.25	1.25	0.06
		WCST Cor	0.075	0.38	
		WCST Per	0.51**	2.5	
		All	0.45	1.0	
Quinsey et al. (1980)	SOC (25) & SO (25) vs. NSO (25)	Trail B	0.37	0.86	0.00
		Raven	0.52	1.21	
		Raven	0.24	0.90	
		SOC vs. NSO	Raven	0.24	
				0.85	

(continued)

Table 1. (continued)

Study	Comparison (N)	Measure	EF	Z	Q
Rimmer (1998)	SO (20) vs. NSO (20)	All	0.21	0.6	9.45**
		Trail B	-0.49	-1.5	
		COWAT	0.18	0.56	
		Raven	0.93***	2.79	
Rubenstein (1992)	Pedo (25) vs. Ctrl (25)	All	0.24	0.9	0.64
		WCST Cat	0.21	0.74	
		WCST Per	0.24	0.86	
		COWAT	0.35	1.21	
		Logical Memory	0.07	0.24	
		Visual Memory	0.34	1.19	
Schiffer and Vonlaufen (2011)	Pedo (15), SOC (15) vs. Ctrl (17)	All	0.92***	3.4	13.11*
	SOC vs. Ctrl	Trail B	0.68*	1.88	
		WCST Cat	0.63*	1.74	
		WCST Cor	0.69*	1.88	
		WCST Per	0.75*	2.04	
	Pedo vs. Ctrl	Trail B	0.18	0.50	
		WCST Cat	1.76***	4.22	
		WCST Cor	1.52***	3.78	
		WCST Per	1.28***	3.30	
Stone and Thompson (2001)	SO (63) Ctrl (60)	All	1.74***	7.9	84.6***
		Trail B	0.73***	3.9	
		WCST Cat	0.77***	4.12	
		WCST Per	1.6***	7.84	
		COWAT	2.89***	11.16	
		Stroop		2.71***	10.86
Suchy et al. (2009)	Pedo (20), SOC (20) vs. Ctrl (20)	All-	0.43*	1.9	7.1
	SOC vs. Ctrl	Stroop		0.26	0.82
		Logical memory	0.54	1.67	
		Visual memory	0.20	0.64	
	Pedo vs. Ctrl	Stroop	1.19***	3.48	
		Logical memory	0.29	0.93	
		Visual memory	0.09	0.30	

(continued)

Table 1. (continued)

Study	Comparison (N)	Measure	EF	Z	Q
Tarter et al. (1983)	SO (14) vs. NSO (28)	Trail B	-0.34	-1.0	0.00
Veneziano et al. (2004)	SO (60) vs. NSO (60)	All	-0.18	-1.0	3.36
		Trail B	-0.29	-1.56	
		WCST Cat	-0.12	-0.68	
		WCST Cor	-0.35*	-1.92	
		WCST Per	0.07	0.42	
		COWAT	-0.23	-1.26	
Westergren (2002)	SOC (41) vs. SO (11)	All	0.11	0.3	0.00
		WCST Cat	0.12	0.35	
		WCST Per	0.10	0.29	
Overall			0.37***	3.18	

Note. EF: Effect size; z: z score; Q: Q score; SOC: Sex Offenders of Children; Pedo: Pedophiles; SO: Sex Offenders; NSO: Non-sex Offenders; HO: Homicide Offenders; Ctrl: controls (nonoffenders); WCST: Wisconsin Card Sorting Task (Cat: Categories achieved; Per: Perseverative errors; Cor: Correct responses); COWAT: Controlled Oral Association Test; I.D.: Insufficient data to calculate z and Q scores.

* $p \leq .05$. ** $p \leq .01$. *** $p \leq .001$.

for neuropsychological results when sex offenders were dichotomized as a function of age of victim although the two groups could still be refined further (e.g., with vs. without physical contact; pedophilic vs. nonpedophilic child molesters; intra vs. extrafamilial victims). The number of available neuropsychological data with more precise subgroups of sexual offenders is still too low to perform such analyses. Comparisons with non-sex offenders were considered next.

Overall cognitive performance of sex offenders versus non-sex offenders. Seventeen independent effect sizes were available between sex offenders and non-sex offenders (violent or nonviolent). As a group, sex offenders again performed significantly lower than non-sex offenders when all neuropsychological tasks were considered together ($d = 0.257$, $SD = 0.004$, 95% CI: [0.128, 0.387], $z = 3.89$, $p < .001$). This time, the distribution of the effect sizes was statistically homogeneous ($Q = 7.95$, $df = 16$, $p > .05$), indicating similarities between populations. Still, homogeneity with non-sex offenders seemed to concern more specifically sex offenders against adults ($Q = 0.64$, $p = .98$; $d = 0.2$, $SD = 0.011$, [-0.007, 0.410] 95% CI, $z = 1.89$, $p > .05$) than sex offenders against children ($d = 0.29$, $SD = 0.084$, [0.127, 0.458] 95% CI, $z = 3.46$, $p = .001$). For this reason, it was decided to further explore the data with individual measures, first compared with the general population, then compared with non-sex offenders.

Table 2. Effect Sizes, Significance (Z), and Heterogeneity (Q) of Neuropsychological Assessments in Sexual Offenders.

E.S.	SD	95% CI	z	Q
Overall				
Sex offenders vs. general population on all neuropsychological measures (k = 14)				
0.59	0.024	[0.29, 0.89]	3.86***	43.58***
Subgroups of sexual offenders				
Child molesters vs. general population on all neuropsychological measures (k = 9)				
0.42	0.01	[0.22, 0.62]	4.41***	11.9
Sex offenders of adults vs. general population on all neuropsychological measures (k = 5)				
0.98	0.23	[0.05, 1.9]	2.06*	10.98**
Trail making-B task (k = 9)				
Sex offenders vs. general population				
0.60	0.007	[0.44, 0.76]	7.32***	8.53
Child molesters vs. general population				
0.28	0.12	[0.04, 0.52]	2.82*	3.93
Sex offenders of adults vs. general population				
0.57	0.18	[0.23, 0.92]	3.23***	2.18
WCST (categories) (k = 9)				
Sex offenders vs. general population				
0.48	0.20	[0.08, 0.88]	4.07**	15.3***
Child molesters vs. general population				
0.48	0.03	[0.14, 0.82]	2.76**	14.3***
Sex offenders of adults vs. general population				
0.53	0.10	[-0.09, 1.15]	1.65	2.35
Stroop (k = 7)				
Sex offenders vs. general population				
0.86	0.006	[0.38, 1.13]	3.49***	65.33***
Child molesters vs. general population				
0.80	0.25	[0.31, 1.30]	3.12***	15.19***
Sex offenders of adults vs. general population				
1.71	1.0	[-0.28, 3.71]	1.69	20.9***
COWAT (k = 6)				
Sex offenders vs. general population				
1.36	0.10	[0.73, 1.17]	5.23***	97.42***
Child molesters vs. general population				
0.39	0.02	[-0.08, 0.64]	1.74	17.36**
Sex offenders of adults vs. general population				
2.54	0.41	[1.73, 3.34]	6.16***	2.50
Comparisons with non-sexual offenders				
Sex offenders vs. non-sexual offenders on all neuropsychological measures (k = 17)				
0.26	0.004	[0.13, 0.39]	3.89***	7.95
Child molesters vs. non-sexual offenders on all neuropsychological measures (k = 11)				
0.29	0.08	[0.13, 0.46]	3.46***	6.86

(continued)

Table 2. (continued)

E.S.	SD	95% CI	z	Q
Sex offenders of adults vs. non-sexual offenders on all neuropsychological measures ($k = 6$)				
0.2	0.01	[-0.007, 0.41]	1.89	0.64
Trail making-B task ($k = 16$)				
Sex offenders vs. non-sexual offenders				
0.02	0.009	[-0.16, 0.21]	0.24	25.9*
Child molesters vs. non-sexual offenders				
0.13	0.11	[-0.11, 0.35]	1.10	18.1*
Sex offenders of adults vs. non-sexual offenders				
-0.23	0.02	[-0.47, 0.02]	-1.83	2.2
WCST ($k = 7$)				
Sex offenders vs. non-sexual offenders				
0.20	0.01	[-0.02, 0.43]	1.79	1.89
Child molesters vs. non-sexual offenders				
0.28	0.05	[-0.16, 0.72]	1.24	1.52
Sex offenders of adults vs. non-sexual offenders				
0.18	0.01	[-0.08, 0.45]	1.34	0.22
Stroop ($k = 5$)				
Sex offenders vs. non-sexual offenders				
0.43	0.03	[0.13, 0.79]	2.71*	5.9
Child molesters vs. non-sex offenders				
0.50	0.04	[0.13, 0.88]	2.62***	5.5
Sex offenders of adults vs. non-sex offenders				
0.11	0.25	[-0.87, 1.09]	0.22	0.22
COWAT ($k = 7$)				
Sex offenders vs. non-sexual offenders				
0.24	0.01	[0.03, 0.45]	2.26*	1.49
Child molesters vs. non-sexual offenders				
0.25	0.01	[-0.09, 0.58]	1.44	0.36
Sex offenders of adults vs. non-sexual offenders				
0.24	0.02	[-0.03, 0.50]	1.74*	1.12

Note. E.S.: Effect Size; SD.: Standard Deviation; CI: Confidence Intervals; z: z score; Q: Q score; k: number of studies; COWAT: Controlled Oral Association Task; WCST: Wisconsin Card Sorting Task.

* $p \leq .05$. ** $p \leq .01$. *** $p \leq .001$.

Cognitive performance of sex offenders versus general population on individual tests. Only four neuropsychological tasks were included in at least four studies comparing sex offenders to the general population: the trail-making B task (time; speed processing and switching; $k = 9$), the WCST (cognitive reasoning and deduction; $k = 9$), the Stroop condition (cognitive inhibition and control of interference; $k = 7$) and the COWAT (vocabulary and verbal fluency; $k = 6$). The validity (more than specificity) of these four tasks is well documented (e.g., Lezak et al., 2012). The distributions of effect sizes for all measures except the trail-making B task (completion time) were

heterogeneous (trail-making B: $Q = 8.53$, $df = 8$, $p > .05$; COWAT: $Q = 97.42$, $df = 5$, $p < .001$; WCST: $Q = 15.3$, $df = 8$, $p = .05$; Stroop: $Q = 65.33$, $df = 6$, $p < .001$). As expected, sex offenders obtained significantly poorer results than controls did on all tasks (Table 2).

Cognitive performances of sex offenders versus non-sex offenders on individual tests. The same four neuropsychological tasks were found in at least four studies that included non-sex offenders as a comparison group (the trail-making B, $k = 16$; the WCST, $k = 7$; the Stroop, $k = 5$; and the COWAT, $k = 7$). This time, the distribution of effect sizes was only heterogeneous for the trail making B, so further analyses were performed only for that measure. As expected, the overall performance of sex offenders did not significantly differ from that of non-sex offenders ($d = 0.0$, $SD = 0.009$, $[-0.164, 0.209]$ 95% CI, $z = 0.238$, $p > .05$; $Q_{within} = 20.2$, $df = 13$, $p > .05$). However, the $Q_{between}$ was significant ($Q_{between} = 5.66$, $df = 2$, $p = .05$), with the between-group difference significant for sex offenders against children (more impairment; $z = 3.46$; $p < .01$) but not for sex offenders against adults ($Z = -1.83$; $p > .05$; Table 2). The last moderator, subgroups of sex offenders, was entered in comparisons with the general population.

Cognitive performance of sex offenders against children and sex offenders against adults versus general population on individual tests. The ANOVA confirmed that, in studies with control groups recruited among the general population, effect sizes for the trail-making B task were similarly distributed across sex offenders against children and sex offenders against adults ($Q_{between} = 2.41$, $df = 1$, $p > .05$; $Q_{within} = 6.10$, $df = 7$, $p > .05$) although the effect might be stronger (higher d and higher z scores compared with the general population, which might indicate greater impairment) for sex offenders against adults ($d = 0.573$, $SD = 0.02$, CI = $[0.226, 0.921]$, $z = 3.23$, $p = .001$) than for sex offenders against children ($d = 0.282$, $SD = 0.03$, CI = $[0.04, 0.524]$, $z = 2.28$, $p < .05$; sex offenders against adults). On the COWAT, the variance was important (Table 2), the effect size distribution was clearly heterogeneous ($Q = 97.42$, $df = 5$, $p < .001$), and the effect appeared to be stronger for sex offenders against adults ($d = 2.54$, $SD = 0.41$, CI = $[1.73, 3.34]$, $z = 6.16$, $p < .001$) than sex offenders against children ($d = 0.39$, $SD = 0.016$, CI = $[0.142, 0.643]$, $z = 1.74$, $p > .05$). On the WCST (category achieved, sex offenders against adults: $d = 0.527$, $SD = 0.10$, CI = $[-0.09, 1.15]$, $z = 1.65$, $p > .05$; sex offenders against children: $d = 0.478$, $SD = 0.03$, CI = $[0.139, 0.817]$, $z = 2.76$, $p < .01$), and the Stroop (sexual offenders against adult: $d = 1.71$; $SD = 1.0$; CI = $[-0.278, 3.71]$, $z = 1.69$, $p > .05$; offenders against children: $d = 0.80$, $SD = 0.25$; CI = $[.0309, 1.295]$, $z = 3.12$, $p = .001$), z scores were significant only for offenders against children (compared with the general population) although that might simply reflect differences in the N because effect sizes seem comparable in each subgroup. Again, the variance was still high and distributions of effect sizes were heterogeneous for both measures (WCST category achieved: $Q = 15.3$, $df = 8$, $p = .05$; Stroop: $Q = 65.33$, $df = 6$, $p < .001$). Next, sex offenders against children were compared to sex offenders against adults.

Between group comparisons. In this meta-analysis, it was not possible to directly and statistically compare the performance of sex offenders against adults to that of sex offenders against children from the same studies because they generally included one group or the other, but not both. In an attempt to compare these subgroups, we randomly assigned each sample of sex offenders against adults to a sample of sex offenders against children with the same task from different studies. According to these exploratory comparisons, sex offenders against adults tended to be better than sex offenders against children on the WSCT ($d = 0.232$, $SD = 0.16$, $CI = [0.053, 0.661]$, $z = 1.70$, $p = .08$), and sex offenders against children were better than sex offenders against adults on the COWAT ($d = 0.521$, $SD = 0.13$, $CI = [0.271, 0.771]$, $z = 4.08$, $p < .001$) and the Stroop ($d = 0.393$, $SD = 0.18$, $CI = [3.55, 4.29]$, $z = 20.7$, $p < .001$). Both groups obtained similar scores on the trail making B ($d = 0.138$, $SD = 0.10$, $CI = [-0.33, 0.058]$, $z = 1.37$, $p > .05$).

Discussion

The first objective of this study was to conduct a comprehensive review of the literature regarding the neuropsychology of sex offenders. Though the number of studies found was impressive ($k = 113$, references with one asterisk in the reference list), nearly half focused exclusively on IQ and only 23 presented results on individual neuropsychological tests and used a comparison group. It could be concluded that the number of neuropsychological studies based on validated tasks and experimental designs (with subgroups) is still very low in the field of sexual deviance.

Our second objective was to demonstrate empirically that sex offenders represent a heterogeneous group from a neurocognitive point of view. As expected, the Q -tests of heterogeneity of effect sizes were highly significant for sex offenders. This suggests that it is preferable to avoid regrouping different types of sexual offenders and/or measures in neuropsychological studies (e.g., Langevin & Curnoe, 2008a; Spinella et al., 2006; Young, Justice & Edberg, 2010). In this study, homogeneity improved when subgroups were considered separately. On one hand, homogeneity might have improved simply as a result of repeatedly fragmenting the sample into smaller groups (although randomly fragmenting the sample would result in similar heterogeneity in the smaller subsamples if heterogeneity was relatively evenly distributed across data sets). On the other hand, other key moderating factors still present might have influenced the heterogeneity of results. These include preferential versus situational types of sex offenders against children and exclusive versus nonexclusive types of pedophiles (Holmes & Holmes, 2009). As the available data were too few for these moderators to be included in the study, future neuropsychological assessments focusing on more refined subgroups of sex offenders should help resolve this question.

Our main goal was to determine whether different subgroups of sex offenders showed different cognitive profiles when individual neuropsychological tasks are used. Unfortunately, only two broad subgroups of sex offenders and a few traditional neuropsychological tests could be included in the meta-analysis. It is clear from the

analyses that sex offenders as a group present significant and wide-ranging cognitive impairments compared with the general population. Interestingly, however, somewhat different cognitive performances were observed when sex offenders against children, sex offenders against adults, and non-sex offenders were considered separately. First, sex offenders against children tended to score lower than sex offenders against adults on the WCST (deduction and cognitive flexibility) although they were significantly better on the COWAT (verbal fluency) and the Stroop test (control of internal interference). These results suggest that different subgroups of sex offenders might present different neuropsychological profiles. Surprisingly, both subgroups obtained comparable results on the trail-making B task although only the time variable (motor speed), not the number of errors (switching capacities) was available. But again, distribution of effect sizes was particularly wide for sex offenders against children. The distinction between nonpedophilic child molesters and exclusive pedophile child molesters, for instance, could be crucial in neuropsychology because the latter seem to be less cognitively impaired (Eastvold et al., 2011; Schiffer & Vonlaufen, 2011; Suchy et al., 2009). Pedophilic child molesters might perform as well as controls (and better than nonpedophilic child molesters) on a wide variety of neuropsychological measures when mean IQ and other socioeconomic factors are similar (Schiffer & Vonlaufen, 2011). In fact, some pedophiles have higher IQ levels and more years of education compared with the general population (Langevin et al., 2000; Lothstein, 1999; Plante & Aldridge, 2005). Other potentially important distinctions such as preferential vs. situational or intrafamilial vs. extrafamilial sexual child abuse should be considered in neuropsychology as well. Given the growing number of neuropsychological studies that distinguish subgroups of sex offenders, it will soon be possible to test hypotheses of the sort (e.g., Cohen et al., 2010; Eastvold et al., 2011; Kruger & Schiffer, 2011; Schiffer & Vonlaufen, 2011; Suchy et al., 2009).

Another interesting result was the confirmation that sex offenders against adults, as a group, tended to score similarly to non-sex offenders (inhibition and verbal deficits). Future neuropsychological studies with more specific measures and participants might find difference between antisocial and deviant sex offenders against adults (e.g. generalized vs. specialized criminality).

If confirmed, results of this study suggest that more specific neuropsychological assessments might also help identify different risk factors associated with sexual offending, such as general delinquency (antisociality, impulsivity, and risk taking) or low social competence (asociality and poor higher order executive functioning). The opposite might also be true, as neuropsychological profiles of high impulsivity scores, low verbal capacities, and poor lower order executive functioning might predict higher risks for general but not sexual recidivism (McCann & Lussier, 2008). To this end, neuropsychological assessments should be based on more specific measures. Traditional tasks such as the WCST, the Stroop, and the trail-making were not developed to assess precise cognitive functions and they are sensitive to various types of cognitive dysfunctions. Higher versus lower order executive functioning could be assessed, for example, using subtests of more specialized batteries (e.g., the Behavioral Assessment of the Dysexecutive Syndrome, or BADS, by Chamberlain, 2003) and specific measures of motor impulsivity (e.g., the CPT-II), behavioral inhibition (e.g.,

the Stop-Signal task), and risk taking (e.g., the IOWA gambling task, the delay aversion task, or the balloon analog task; see www.millisecond.com for computerized versions of these tests). Specific measures of verbal learning and memory (e.g., California Verbal Learning Task or CVLT-II by Delis, Kramer, Kaplan, & Ober, 2000) could help discriminate between subgroups of sexual offenders as well, given that these faculties are more closely linked with antisociality than with asociality.

Overall, this first meta-analysis of existing neuropsychological results regarding sex offenders yielded some interesting findings although available data were too few to test or confirm all of the hypotheses. The main goal was to define specific subgroups of sex offenders based on criminological typologies and to demonstrate that they present distinct cognitive profiles. Unfortunately, it was not possible for us to achieve this goal. Consequently, it is currently impossible to say whether sex offenders present broad, nonspecific cognitive impairments or, instead, specific neuropsychological profiles. Besides limitations associated with meta-analyses in general (e.g., the file-drawer problem, publication bias, unequal methodological qualities across studies, subjective coding of variables; for a review see Lipsey & Wilson, 2001), the present study is based on few studies with numerous limits. Among these limits are file-based data collection, neuropsychological assessments for clinical purposes with different examiners, participants recruited exclusively in institutional settings, high rates of refusals, different testing procedures, inclusion of unmatched comparison groups (age, gender, education, cultural background, etc.), and inclusion of highly different individuals in a single group (sadistic persons vs. gang members; serial rapists vs. exhibitionists, asocials vs. antisocials, etc.). Future neuropsychological investigations should consider these limits and include subgroups of offenders based on criminological and psychological typologies as well as validated and specific cognitive measures (for a good example, see Schiffer & Vonlaufen, 2011). In time, neuropsychological evaluation could help specify diagnoses, determine specific risk factors, and estimate recidivism risk for individual sex offenders.

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Note: *References marked with an asterisk indicate studies found in the literature search. References marked with three asterisks indicate studies included in the meta-analysis.*

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Neuropsychological Functioning Among
Violent and Nonviolent Sex Offenders

by

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ABSTRACT

Violent sex offenders, nonviolent sex offenders, violent non-sex offenders, and nonviolent non-sex offenders were compared on neuropsychological testing and on personality testing. A neuropsychological test battery and the Minnesota Multiphasic Personality Inventory - 2 (MMPI-2) were administered to 93 and 50 male felons respectively. Subjects were drawn from a data base provided by the state Department of Corrections. Potential indicators of neuropsychological impairment were controlled during the selection process. Analyses of Variance ($\alpha=.05$) found that violent sex offenders scored significantly lower than the other three groups on two measures that are sensitive to left hemisphere impairment and one that assesses right hemisphere impairment suggesting a more diffuse, rather than a lateralized mode of functioning. Non-violent sex offenders scored higher than the other groups on four of the fifteen neuropsychological measures and higher on three additional measures than two of the other three groups. Results also indicated that violent non-sex offenders may better process information with the left hemisphere. On the MMPI-2, violent sex offenders scored higher on Scale F and nonviolent sex offenders scored lower on Scales F and 9. It would appear that information regarding neuropsychological functioning may be useful in identifying more appropriate approaches to intervention for different groups of offenders. Implications for treatment are presented.

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Introduction

Violence is a social problem that increasingly affects a large number of individuals in the United States. Approximately two-thirds of all attempted acts of violence are actually completed. According to Bureau of Justice Statistics, Americans were the victims of 15.4 million crimes in 1990. Persons age 12 and older experienced six million violent victimizations, a rate of 30 victimizations per 1000 individuals. A 1987 survey (Blum) indicated that violence in the United States has replaced communicable diseases as the primary cause of mortality in young people during the past 30 years. Homicide deaths have increased 300% to become the number two killer, after accidents, of 15- to 24-year olds. Additionally, statistically significant increases in the estimates of rape occurred in 1991, with one rape per 1,000 persons over the age of 12.

These unfortunate statistics have resulted in a penal system strained by the sheer number of inhabitants. In July, 1990, the United States Department of Justice released figures indicating that, in 1988, the average monthly payroll in the federal judicial system was \$3,680,457. Of this amount, \$1,036,628 was spent by corrections with the remainder being disbursed for police protection and the judicial process. Not included in this figure is the cost of maintaining criminals in correctional facilities. In 1990, the average cost per inmate incarcerated in state

facilities was \$15,513.

Violent behavior is a phenomenon that has been widely studied by social, behavioral, and biological scientists. In spite of the degree of attention it has been afforded, however, violence has defied easy solution in terms of adequate understanding and prediction, and in effective prevention. It has proven consistently resistant to treatment, as well.

Social and Environmental Influences

In the last decade, research on sexual assault has increasingly shifted from a clinical and criminologic orientation toward one that is epidemiologic (Finkelhor & Lewis, 1988). The shift has been paralleled by one or more social-psychological concepts. Talk of sociopaths, the criminal personality, pedophilia, sadism, and masochism is giving way to talk about rape myths, substance abuse, media exposure, and attitudes and beliefs. The social-psychological concepts being used to analyze sexual assault appear to grow out of the following assumptions:

1. Social, and peer groups (the latter often accompanied by substance abuse) and social institutions, such as the media, are influential in fostering sexual assault.
2. Sexual assault behavior, although discouraged by some social sources, receives endorsement and support from others. This support is an important factor in

explaining individual behavior.

Early Experiences

Researchers and professionals have used the phrases "cycle of violence" and "intergenerational transmission of violence" loosely to refer to assumptions or hypotheses about the consequences of abuse and neglect in relation to a number of different outcomes. Others focus on the relations between child abuse and neglect and later criminal behaviors by both juveniles and adults. Widom, (1989) reviewed all cases of physical and sexual abuse and neglect processed during the years 1967 through 1971 in a county juvenile court (situated in a metropolitan area in the Midwest). Nine-hundred-eight cases of abuse and neglect processed in adult criminal court in which the victim was 11 years of age or less were selected for inclusion in her study. A control group, matched as closely as possible on the basis of sex, age, race, and approximate family socioeconomic status during the time period under study, was chosen from among the ranks of elementary school children. Findings indicated that abused and neglected children had a higher likelihood of subsequent arrests for delinquency, adult criminality, and violent criminal behavior than the matched controls. As expected, victims of physical abuse had the highest level of arrests for violent criminal behavior. According to the author, these results provide strong support for the cycle of violence hypothesis.

Koss and Dinero (1988) surveyed 2,972 male college students regarding their use of several degrees of verbal coercion and physical force to obtain sexual intimacy with women without consent. The most severe form of sexual aggression reported by each subject was used to classify them into one of five groups: sexually nonaggressive, sexual contact, sexual coercion, attempted rape, and rape. Subjects also provided data that were grouped into three blocks of variables: early experiences, psychological characteristics, and current behavior. Results support a developmental sequence of sexual aggression in which early experiences and psychological characteristics establish preconditions for sexual violence. In turn, these preconditions are most likely to be associated with self-reported sexual aggression when linked to the presence of releasing factors in the current environment.

In 1985, Langevin, Paitich, & Russon administered the Clarke Parent Child Relations (PCR) Questionnaire to 40 rapists, 40 nonviolent sex offenders (exhibitionists-voyeurs, hereafter sexual anomaly group), 40 normal controls, and 25 non-sexual assaultive offenders. The assaulters and rapists reported the most similar pattern of parent child relations. The largest effect was a lower identification with mother, but there was also a prominent, if less powerful, effect showing lower father identification as well. Fathers of assaulters and rapists appeared to be

aggressive toward mother and son with the latter reciprocating. The offenders reported that, in their childhood, affection received from both parents was low while their strictness was high. The sexually anomalous and rape groups were similar in reporting that their mothers were less affectionate to them and that both parents were less indulgent to them than reported by the other groups. Individual supplementary items from the Clarke PCR indicated that, compared to non-assaulters' parents, both the assaulters' and rapists' fathers were more often in trouble with the police and both their fathers and mothers were often drunk. The offenders followed in their footsteps, indicating at admission that they drank too much. Rapists and assaulters more often ran away from home as children. There was no evidence of parental sexual abuse or incest but the assaulters more often overheard parents having sex than controls did. They were also more likely to be jealous of a sibling who was father's favorite although that sibling was not necessarily a male.

Langevin, Hucker, Handy, Purens, & Russo (1985) administered the Clarke PCR to four groups of men consisting of 32 heterosexual pedophiles, 40 homosexual pedophiles, 40 bisexual pedophiles, and 54 community controls. Only six of the 16 PCR scales yielded significant differences, but four of the six were mother scales and two were father scales. Mothers were reported to be more aggressive and stricter by

heterosexual and bisexual pedophiles than by the other two groups. However, there was considerable overlap of group scores. Mothers in all pedophilic groups were reported as less affectionate than mothers of controls were. The largest differences among the groups were in mother identification. Heterosexual and bisexual pedophiles identified less with mother than the other two groups did. The father scales were not as discriminating as the mother scales, with father identification marginally weaker in pedophilic groups than in the controls. Fathers of bisexual pedophiles were reported to be more indulgent than fathers in the other three groups. The heterosexual and bisexual pedophiles had more mothers with a history of psychiatric hospitalization.

Lang & Langevin (1991) examined the extent to which disturbed parent-child relations distinguish aggressive sex offenders from non-aggressive sex offenders. The authors hypothesized that pedophiles and incest offenders who used physical force in their offenses would be more likely to show disturbed father-son relationships involving aggression than those who did not use force. One hundred eighty-one men were compared on parent-child relations, using the Clarke PCR. The sample included 66 heterosexual pedophiles, 29 homosexual pedophiles, 36 incest offenders and 50 controls. The offender groups were further identified by those who used force (20%) versus those who did not; into

those sexually victimized as children themselves (53%) versus those not victimized; and into those physically abused as children (47.5%) versus those not abused. Significantly more offenders who were both sexually and physically abused as children showed more disturbances in father relationships than offenders who were not abused during their childhoods. Collectively, sex offenders' fathers were considered more aggressive and more strict, but viewed as more affectionate to their sons. The sex offender groups identified with their fathers, but homosexual pedophiles were less inclined to do so. Only one Mother scale was significant: Aggression to Fathers. There was a trend for mothers of sex offenders in general to be more aggressive to their husbands, but not to their sons.

Substance Abuse

Alcohol has been reported to play a role in violent acts, including sexually aggressive ones. It has been implicated in about half of known rapes and in some nonviolent sexual crimes. Bain, Langevin, Wortzman, Hucker, Dickey, & Wright (1988) examined 461 male sex offenders' histories of alcohol and drug use. Subjects completed a drug survey, the Michigan Alcoholism Screening Test, and a drug abuse screening test. Most subjects had used alcohol and tried a wide range of drugs. Over half of the subjects had tried at least one street drug; marijuana being the most frequent. Over half of the subjects were alcoholics, but

less than one-fifth had a drug abuse problem. Although the majority reported positive affect in conjunction with alcohol and drug use, one-fifth to one-half reported depressed affect. Use of alcohol and amphetamines was most associated with hostile feelings, and amphetamine and hallucinogen use was most associated with paranoia. Subjects felt most out of control with cocaine and hallucinogens.

Christie, Marshall, & Lanthier (1978) found 65% of their pedophilic prison sample, and 56% of rapists, were problem drinkers or alcoholics. These findings revealed a high incidence of alcohol abuse compared to Canadians in general. In addition, 50 percent of the pedophiles and 58% of rapists noted that one or both of their parents were alcoholics or had serious drinking problems. At the time of the offense, 53% of pedophiles and 56% of rapists were noticeably intoxicated and 23% of pedophiles and 24% of rapists were drinking just prior to the offense. Nine percent of pedophiles and 18% of rapists were using drugs, mostly marijuana or prescription tranquilizers. Approximately half of pedophilic and other sexual offenders against children studied by Rada (1976) reported that they had been drinking at the time of their offense, suggesting that substance abuse may have played some role in the offenses.

Media

Over the past years, most noticeably since the advent of broadcasting, there has been debate concerning the effects of sexually explicit materials presented through the media. In 1967, the United States Congress determined that pornography was a matter of national concern and established the Commission on Obscenity and Pornography to investigate the issue. After reviewing the available research, the Commission concluded that there was no evidence that pornography had antisocial effects. Subsequent research contradicts the Commission's conclusions. Malmuth and Donnerstein (1982) described a series of experiments on the effects of aggressive pornography on behavioral aggression. They identified a variable (i.e., the outcome dimension) which seems to be of importance in explaining the contradictory findings concerning sexual responsivity to aggressive pornography. They cite data indicating that the reactions of the victim in rape scenes significantly affects the sexual arousal exhibited by members of the audience. If the victim was portrayed as becoming involuntarily sexually aroused by the assault (positive outcome), the subjects showed levels of sexual arousal both on self-reports and on penile tumescence measures, that were at least as high as those stimulated by mutually consenting depictions (Malmuth, 1980; Quincy & Chaplin, 1981). Rape portrayals that depicted the victim as continuously abhorring the experience

(negative outcome) resulted in significantly less sexual arousal than mutually consenting themes.

Malamuth & Check (1985) classified males as high likelihood to rape (HLR) or low likelihood to rape (LLR), based on their answer to a question asking their likelihood to rape if they knew they would not be caught. In Part 1, men read one of several versions of a sexually explicit story, including a rape story in which the victim becomes aroused. In Part 2, subjects were exposed to a realistic rape story in which the victim suffers. The authors found that all males exposed to the positive rape story, regardless of whether they were HLR or LLR, attributed more pleasure to the female victim in the second rape story. The groups did differ on two additional questions asked by the experimenters: What percentage of women would enjoy being raped; and what percentage of women would enjoy being forced into sex? 37% of the HLR men who had been exposed to the rape/arousal story in Part 1 reported that women would enjoy rape, and 38% reported that women would enjoy being forced. Donnerstein, Linz, & Penrod (1987) suggest that the above results are important because they suggest that the effects from exposure to aggressive pornography may be dependent upon an individual's initial attitudes about rape and other forms of violence against women. This may indicate that exposure to aggressive pornography is not necessarily "causing" positive attitudes about rape, but rather

reinforcing and strengthening already existing beliefs and values.

Legitimization of Violence

Most American homicides arise out of social conflicts between acquainted people. Daly and Wilson (1989) suggest that homicides in the United States are sufficiently numerous that one can expect transient effects of violent publicized events upon daily homicide rates. They offer as an example the research by Phillips (1983) who found a significant increase in homicides occurring a few days after heavyweight championship boxing matches. The authors state that Phillips adopted a naive view of homicide that ignores its social context. They suggest instead that young men who are already of a competitive, combative mind set identify with prizefighters, are rendered somewhat more belligerent by the aggressive dialogue surrounding the fight and are, therefore, likelier to end up dead in an escalated personal confrontation during those days when the fight is still a popular topic. Wilson and Daly offer the legitimization of violence as a more plausible explanation. When acts of violence occur and more particularly, when at least some such acts are seen to be socially acceptable, then general attitudes toward the use of violence shift in the direction of acceptance and thresholds for resorting to violence fall. Archer and Gartner (1984) consider such a legitimization process to be the likeliest explanation for postwar

increases in homicide rates. Using data on homicide rates in various countries before, during, and after various wars, these authors have provided the first truly convincing demonstration that such increases are indeed the rule. After considering various competing explanations, the "legitimation of violence model" proved to be the most viable.

Barron & Straus (1988) examined the relationship between cultural support for violence and the incidence of rape in the 50 states and the District of Columbia. Two measures were used to test the theory that, within the United States, the large differences between states are partly the result of state-to-state differences in cultural support for non-sexual and legitimate violence. They refer to their hypothesis as "cultural spillover theory". The distinctive feature of this theory is the concept that cultural support for rape may not be limited to beliefs and attitudes that directly condone rape and other criminal violence. There could be cultural elements that indirectly legitimize sexual violence. The central proposition of the theory is that the more a society tends to endorse the use of physical force to attain socially approved ends - such as order in the schools, crime control, and military dominance - the greater the likelihood that this legitimization of force will be generalized to other spheres of life, such as the family and relations between the sexes,

force received less approval. A structural model of the cultural spillover theory was tested using the Legitimate Violence Index. The indicators included in this index were selected on the assumption that if there are group differences in values concerning violence, this should be observable in many different activities, including education, recreation, and law enforcement. The indicators included in the Legitimate Violence Index are mass media, governmental use of violence, and participation in legal or socially approved violent activities. Results were replicated using the Violence Approval Index. Because it is based on directly expressed attitudes regarding circumstances under which it is appropriate to use physical force, the Violence Approval Index differs from the Legitimate Violence Index. More specifically, it is based on the percentage of persons in each state who endorsed the use of violence under each circumstance. A theoretical model hypothesizing the relationship of these two measures of legitimate violence and seven control variables to rape was developed and tested using path analysis. The results show that legitimate violence is directly related to the rape rate. The degree of social disorganization, urbanization, and economic inequality, coupled with the percent of single males, are also directly related to rape. The population's youthfulness and percent of blacks affect rape indirectly through their association with legitimate

violence. States that are high in respect to legitimate violence tend to have a larger representation of men in the violence-prone ages of 18-24 and a higher proportion of black residents. It was also found that legitimate violence is more prevalent in rural states and in states that have a disproportionate number of divorced and single men. Of the eight independent variables, the percent of males divorced emerged as the most powerful predictor of rape. The authors argued that, since marital dissolution represents a significant disruption in an individual's life, it could be argued that a heavy concentration of divorced men contributes to a social context that is conducive to rape, and/or, that divorced men tend to harbor feelings of anger, contempt, and hostility toward their estranged spouses. These feelings may become generalized to other women as well and create a climate of antagonism between the sexes. Whatever the underlying processes, it is clear that a large proportion of divorced men increases the risk of rape.

While these studies suggest that aggression can also be induced by social and environmental influences, it is important to stress the fact, however, that the effect of these influences depends to some extent on the environmental setting and the mental "set" of the organism (Elliott, 1987).

Personality Influences on Violence

Early twentieth century interest in sex and aggression is reflected in Freud's writings. His investigations concerning human behavior focused on sex during his early years as a psychoanalyst and, only much later, on aggression (Stone, 1991). Among the earliest references to aggression is the comment in the "Three Essays" (1905) on sadism and masochism. Aggression, at this stage of Freud's thinking, was intimately bound up with masculinity, with sadism and with being "active" (including sexually assertive) (Freud, 1905), while "feminine" was equated with masochism and with being "passive." Freud continued to speak of an interweaving of sexual and aggressive tendencies, but not until later did he give aggression equal status and develop a dualistic model. In 1940, he wrote of the commingling of the sexual and destructive instincts. He described sex as "an act of aggression with the purpose of the most intimate union."

A contemporary psychoanalyst proposes that violence, i.e., the pathology of aggression, is peculiar to mankind (Stone, 1991). He believes that this difference is accounted for by man's unique ability, thanks to memory and language, to think about the past and the future. He continues that, over and above temporal lobe epilepsy, serotonin deficiency, or hyperandrogenization that may provoke violent outbursts, there is learning and

anticipation. Ethnic and racial prejudice can be taught and abusive rearing can instill in one the tendency to aggress against others. Stone describes humans as ironical creatures; intensely social, unable to survive except as part of a group; with prodigious memories, and able to contemplate their own fate and death. He concludes that "much of what is terrible about us is simply the darker side of our own unique gifts" (pg. 521).

Fagan, Wise, Schmidt, Ponticas, & Marshall (1991) compared personality profiles of 51 men with sexual dysfunction to those of 51 age-matched men with a primary diagnosis of paraphilia employing the NEO Personality Inventory (NEO-PI), a measure of the five-factor model (McCrae, 1989). The principal finding that the sexual dysfunction and paraphiliac groups have different profiles on the five-factor model of personality suggests that there are stable personality features about each group. The men with sexual dysfunction had an essentially normal group personality profile. The paraphiliac men were significantly higher on Depression, Hostility, and Impulsiveness. They also reported lower Warmth and higher Fantasy.

Two major factors considered to be important in rape were examined by Langevin, Paitich, & Russon (1985): history of aggression and the presence of sexual anomalies. They hypothesized that if the rapist is basically an assaultive person he should be more similar to the common assaultive

group than to the other two groups. If he is sexually unusual rather than aggressive, he should resemble the nonaggressive sexually anomalous group more than the other two groups. If, however, rape is a fusion of aggression and sexual anomaly, there should be an interaction effect for the dependent variables in the analysis so the rapist is different from all the other groups although sharing features with both. The subjects, consisting of 40 rapists, 40 nonviolent sex offenders, 40 normal controls, and 25 nonsexual assaultive offenders, were administered the Minnesota Multiphasic Personality Inventory (MMPI). The strongest, most consistent finding was the similarity of rapists to the assaultive groups. Both groups tended to be depressed, suspicious, ruminating, worrying, confused, and higher in energy compared to non-assaultive groups. Rapists contrasted with assaultive men in having more bodily concerns, being more feminine, less energetic and more introverted. Only in the case of the Paranoia (Pa) Scale did the assaultive and rapist groups differ; the assaulters were significantly more paranoid than rapists and both were more paranoid than the nonviolent groups.

Panton (1978) compared the MMPIs of three groups of incarcerated offenders: 30 had been convicted of raping adults, 20 of raping children, and 28 non-violent child molesters. There were no significant mean scale differences between the profiles of the two rapist samples, both

implying aggravated hostility, resentfulness, social alienation, self-centeredness, and the impulsive seeking of immediate gratification. In contrast, the child molesters were self-alienated, had low self-esteem, self doubt, anxiety, were inhibited regarding acts of aggression, had an aversion to violence, a need for reinforcement from others, and feelings of inadequacy, insecurity, and fear of heterosexual failure. The motivation of the two rapist groups appeared to be more assaultive than sexual whereas the motivation of the molester group appeared to be the satisfying of sexual needs at an immature level of sexual development. The two rapist samples were considered to be of equal aggressive pathology which appeared to imply that the choice of the victim was more likely to have been a matter of immediate availability rather than a factor of the victim's age. In contrast, the choice of the victim by the child molester appeared to have been the result of the offender cultivating a relationship with a young child for the purpose of inducement precipitated by the child molester's fear of rejection and failure in adult heterosexual advances. Based on the profile configuration of the child molesters, there appears to be little danger of their resorting to violence should their sexual advances be resisted or rejected by the children involved. In contrast, the predominance of aggressive sociopathic characteristics, as demonstrated by the profiles of the adult and child

rapists, appear to support the contention that these individuals would not likely hesitate to resort to violence in order to achieve their immediate goals. The results also support the contention that the actual rape may have been the by-product of an assault initially motivated by some non-sexual connotation, whereas the motivation of the molesters appears to have been the satisfying of sexual needs. Since the results of the present study found both rapist groups to be of equal aggressive pathology, it is contended that the choice of the rape victim was more likely to have been a matter of immediate availability of the victim rather than age. On the other hand, the choice of the victim of the child molester was likely to have been the result of premeditated inducement.

Sex offenders and treatment modalities are currently matched as a function of a legally based distinction between child molesters and rapists. Hillbrand, Foster, & Hirt (1990) examined the validity of this match by comparing groups of child molesters and rapists using psychiatric, psychological, and psychosocial measures in order to determine whether these two groups actually differ clinically. Subjects were 29 male sex offenders from a Northeastern state forensic hospital. Twenty-eight subjects had been convicted of sexual assault and/or risk of injury to a minor; one subject had a well-documented history of pedophilia, yet had never been convicted. Their findings

suggest that child molesters and adult rapists constitute two distinct clinical groups. Elevated scores on measures of Insecurity, Psychological Inadequacy, Paranoia, Depression, and Passive Response to Threat, indicate that adult rapists suffer from more severe psychopathology than child molesters. These findings are at variance with the popular stereotype of the rapist as a self-assured, guilt-free, sadistic psychopath whose pathology is characterized by disinhibition. Rather, they portray the rapist as suffering from dysphoria and inadequacy, i.e., psychopathology characterized by inhibition and subjective distress.

Using the MMPI, Langevin & Watson (1991) compared 79 biological and 43 stepfathers who committed incestuous acts on their daughters. There were 79 biological fathers and 43 stepfathers. The authors noted that a higher proportion of stepfathers should have been obtained since stepfathers are reported as more likely to sexually abuse their daughters. Langevin and Watson suggest that their sample may reflect referral practices of community agencies and lawyers for treatment. The MMPI was examined for 125 derived scales which may be important in sex offenders i.e., sexual deviance, substance abuse, violence, defensiveness, personality and brain damage. Six scales would be expected to be significant by chance, but only three were; two measures of alcoholism and one defensiveness measure,

Suspiciousness. There were no significant differences between the two groups.

Langevin, Hucker, Handy, Purins, & Russon (1983) were interested in studying the personalities of bisexual pedophiles. Langevin, et.al. found that the more types of sexual preferences an individual had, the more emotionally disturbed his personality was, as measured by the MMPI. Bisexual pedophiles, for example, are of particular concern because they show sexual reactivity to both sexes. Four groups of men were in the study: 32 heterosexual pedophiles, 40 homosexual pedophiles, 16 bisexual pedophiles, and 54 community controls. All research participants were administered the MMPI. The results indicated considerable emotional disturbance among pedophiles. The Hypochondriasis, Depression, Psychopathic Deviate, Paranoia, Psychasthenia, Schizophrenia, and Social Introversion scales were significant in the group comparison. In five of those seven scales, there were no significant differences among the pedophilic groups but all scored higher than controls. In the cases of Hypochondriasis and Depression there was considerably greater overlap of scores with controls. Most of the difference between pedophilic groups and controls appeared on the psychotic scales. Serious emotional disturbance, confusion, rumination, and suspicion characterized all the pedophilic groups; thus there was significant clinical pathology among these groups.

Ideally, there would be an MMPI profile type associated predominantly with sex offenders. Empirical research, however, has indicated that personality is as varied among sex offenders as it is in the general population (Velasques, Callaghan, & Carillo, 1989). The use of the MMPI to identify personality traits related to criminality, in particular the antisocial personality, is problematic (Langevin, Wright, & Handy, 1990). DSM III diagnoses of antisocial personality may reflect long term criminality, which is not consistent with the diagnosis of psychopathic personality, as used in the development of the MMPI Psychopathic Deviate (Pd) Scale. The Pd scale was constructed using a criterion group of young persons between the ages of 17 and 22 diagnosed as psychopathic personality, asocial and amoral type, who were referred for testing by the courts because of their delinquent activities. None of the criterion cases was a major criminal type. The criterion group included more females than males, who engaged in delinquent behavior without planning and with little effort to avoid being caught. This scale has a mixture of items referable to criminal behavior but also family problems. It follows that the PD scale is often elevated in the criminal population but this does not necessarily indicate a high percentage

more attuned to discerning the antisocial personality, has been the Megargee, Cook, and Mendelsohn (1967) Overcontrolled Hostility (OH) Scale. Other MMPI derived scales have been developed to examine hostility, aggression, and violence, but they have not received the attention the OH Scale has (Langevin, Wright, & Handy, 1990). McCreary (1975) found that the Authority Conflict Scale, but not the OH scale differentiated child molesters with one or more previous arrests from those with no prior arrests. Deiker (1974) examined 17 experimental MMPI derived scales of hostility and control and 4 response bias scales in 168 male criminals assigned to 4 levels of aggressiveness. He found that all but one of the 17 scales differentiated the groups. These results suggest that the MMPI may be of value in distinguishing violent and nonviolent sex offenders.

Langevin, Wright, & Handy (1990), utilizing a data base of 479 sex offenders and community controls, examined six measures derived from the MMPI that assess brain damage. The data base was comprised of 14 exhibitionists, 39 homosexuals, 31 bisexuals, 29 heterosexual pedophiles, 22 homosexual pedophiles, 46 transsexuals, 27 incestuous men, 217 multiple deviants, and a control group of 54 men. Four scales had alpha over .70 and two, Brain Lesions and Neuropsychiatric Hospitalization Chronicity, were .18 or less. Five scales discriminated the offender and control groups but the Brain Lesion Scale, with only five items, did

not. Discriminations for Caudality and Epilepsy were close to chance level. No scale correlated with L,F, or K or with age. Most were moderately correlated with education and IQ, as might be expected. The authors point out, however, that the correlations were modest, suggesting these scales might have practical application.

Biological Influences on Violence

Perinatal and postnatal complications

Considerable evidence indicates that many biological and developmental disorders (e.g., reading and learning disabilities) associated with delinquency and crime may be attributable, in part, to central nervous system (CNS) dysfunction which is linked predominantly to complications occurring before and immediately after birth (for reviews, see Denno, 1982, 1985). Infants at risk - those born prematurely, with low birth weights, etc. - seem to have somewhat more difficulty adjusting to poor environments than healthy, full-term infants. It appears that the relatively less mature, or more stressed, central nervous systems of these infants are less able to become integrated in deprived circumstances (Eagle & Brazelton, 1977).

At-risk infants are not only more vulnerable to their immediate environment, they are also more prone to later CNS related disorders, including those associated with crime. These disorders include reduced intelligence or achievement, attention deficit disorder and hyperactivity, problems

associated with cerebral dominance, and learning and reading disabilities (Denno, 1982). Unfavorable environmental circumstances during childhood, such as large family size, absence of the father, late birth order, and low socioeconomic status may compound these disorders (Denhoff, Hainsworth, & Hainsworth, 1972). Likewise, CNS related deficits accompanied by subcultural or familial deprivation may impair social bonds (Denno, 1990).

A number of studies have related perinatal factors to later criminal and violent behavior. Litt (1971), in a study of 1944 consecutive births in a Danish hospital between 1936 and 1938, found perinatal trauma to be predictive of impulsive criminal offenses. Lewis, Shanok, & Balla (1979) found seriously delinquent incarcerated children to be more likely to have sustained perinatal trauma than nonincarcerated delinquent children. Similarly, Mungus (1983) found that perinatal factors were significantly related to violence in a group of psychiatric patients.

Infections

The psychopathic type of aggression has also been reported as a sequela to viral infections, which have a special impact on the limbic system of the brainstem (Wilson, 1960). This was particularly notable in the encephalitis lethargica epidemic (1917 to 1925), in which the disease apparently contributed to delinquency in

previously normal children and adolescents. (Elliott, 1987).

Vagotonia

Venables (1988) developed a new theory of violence that argues that violent offenders have an autonomic nervous system that is vagotonically tuned (i.e., favoring parasympathetic, as opposed to sympathetic, autonomic nervous system processes). Low heart rate has been found to relate to criminal and violent offending in a number of studies (Farrington, 1987; Raine & Venables, 1984; Raine et al., 1990). Venables (1988) argued that low heart rate in violent offenders reflects an excess of vagotonia and "fearlessness," which may account for the lack of inhibition of aggressive behavior. Raine & Scerbo (1991) believe that support for Venables' idea can be found in bomb disposal experts who have been decorated for their bravery and who also have significantly lower heart rates than both undecorated bomb disposal experts and soldier controls (Cox, Hallam, O'Connor, & Rachman, 1983).

Violent, aggressive behavior has also been related to dietary factors and reactive hypoglycemia (see Venables & Raine, 1987 for a review). Violent offenders with psychopathic features have demonstrated a high level of insulin secretion and are consequently more prone to insulin-induced hypoglycemia (VirKunnen, 1983). VirKunnen (1986) has found that violent offenders with a history of alcoholism are particularly characterized by reactive

hypoglycemia. Increased irritability is one symptom of hypoglycemia (Marks, 1981), and this could be a factor in the development of an aggressive outburst. Venables (1988) has integrated the diverse findings of lowered heart rate, hypoglycemia, and EEG underarousal in violent offenders by arguing that the concept of vagotonia can explain all three sets of results. Since stimulation of the vagus nerve leads to hypoglycemia via release of insulin from the pancreas, increased vagal tone in violent offenders would also be consistent with the finding of hypoglycemia in such populations (Virkkunen, 1983).

Genetics

The XYY chromosomal anomaly was thought for many years to predispose individuals to violent criminal behavior and to be associated with high levels of plasma testosterone. However, according to Elliott (1988), the correlations are not consistent and some geneticists consider the issue unsettled. A more important development is the discovery of a structural abnormality of the X chromosome associated with mental impairment from retardation to low normal intelligence, with learning difficulties, and with behavioral problems such as hyperactivity, violent outbursts, and autistic symptoms.

The peak incidence of physical violence in the home or in the streets is in late adolescence and early adult life (Bureau of Justice, 1992). Even after the age of 50,

however, pathological violence can occur for the first time in a formerly non-aggressive individual as a result of an organic brain insult, intoxication, or psychosis (Elliott, 1988). One link between youth and violence is related to androgen (e.g., testosterone) levels in both males and females, (Moyer, 1976) but there are other factors to be considered. For example, some people mature faster than others and do not acquire an adult level of self-control, foresight, judgment, and social conscience until middle age (Elliott, 1988). These functions are largely mediated by the associational neocortex of the frontal and temporal lobes, which is the last to mature in terms of myelination. This process may not be complete until the third or fourth decade (Yakovlev & Lecours, 1967). There is no information as to the rate of maturation in neurotransmitter systems but there is evidence that the formation of new synaptic connections, which are necessary for learning, can continue in the human brain until advanced ages. There also is a persistence of the bilateral slow waves of childhood in the electroencephalograms of many aggressive adult psychopaths. This is consistent with the theory of maturational lag advanced by Kraepelin (Elliott, 1988).

Males are more often prone to violence than are females in primates (including humans) and other animals (Elliott, 1988). The author further states that there are gender determined differences in brain anatomy, cognitive skills,

speed of maturation, and behavior. As a result, males are more susceptible to conditions that can be warning signs of pathological aggression. These include episodic dyscontrol syndrome, attention deficit disorder, and antisocial personality disorder.

Endocrine Abnormalities

The majority of studies available on sex hormones in sexually anomalous men have been done on homosexuals (see Bain & Langevin, (1985) for a review) with only a few studies of sexually aggressive heterosexuals and pedophilic offenders. Langevin, Hucker, Dickey, Wright, & Schonberg (1988) examined 26 men who had been referred for assessment and treatment in reference to a sexual offense against male and female children. A control group of 16 nonviolent non-sex offenders was used for comparison with pedophiles and served to control for offender and patient status. The controls faced charges, or were convicted, of fraud or property offenses. The subjects were compared on baseline values of Lutenizing hormone (LH), follicle stimulating hormone (FSH), testosterone, estradiol, dehydroenpiandrosterone sulphate (DHEAS) and cortisol. Pedophiles had significantly higher levels of LH and FSH but lower levels of testosterone. There were no significant differences on the remaining hormones. When age and substance abuse were controlled, LH and FSH differences were not statistically significant but testosterone differences

remained and pedophiles then demonstrated lower levels of cortisol. In a second study, 26 pedophiles and 14 healthy community controls were compared on the gonadotropin releasing hormone (GnRH) test. Blood was sampled for LH and FSH at intervals of 0,15,20,45,and 60 minutes after injection of GnRH. There were no group differences in baseline values of LH or FSH. Pedophiles, however, showed greater increases in LH (but not FSH) than controls after GnRH injections. Results were similar when age, substance abuse and baseline levels of testosterone were taken into account.

The administration of testosterone increases aggression in both sexes, while castration reduces sexual and irritable aggression in males (Kolb & Wishaw, 1990). In one study, higher levels of testosterone were found in violent female felons than in nonviolent control subjects (Ehlers, Rickler, & Hovey, 1979). Additionally, androgen suppressing drugs can reduce male urges to commit sexual offenses against children (Moyer, 1976).

Langevin, Bain, Wortzman, Hucker, Dickey, & Wright (1988) examined sex hormone profiles in 49 cases of sexual aggression and 31 controls. The results suggested that the adrenal axis of the endocrine system might be important in sexual sadists and nonsadistic sexual aggressives. The weak androgen, DHEAS, was found to be elevated in sexual aggressives generally, versus a control group of nonviolent,

non-sex offenders matched for age and education. There was a trend for cortisol to be higher, and prolactin lower, in sexual aggressives, as well. Testosterone, however, was not significantly different in these groups. The nonsadistic sexual aggressives had higher levels of testosterone than the sadists or controls. The authors attributed this latter finding to the results of sex hormone analyses in aggressive groups being frequently confounded due to their high incidence of substance abuse.

Studies of the cerebrospinal fluid (CSF) serotonin metabolite (5-HIAA) in depression, impulsivity, and violence can generally be divided into five groups: pharmacologic studies, CSF studies, postmortem studies, neuroendocrine studies, and family-genetic studies. A number of these indicate that functions of the central serotonergic system (5-HT) may be altered in humans with aggressive/impulsive behaviors. According to Brown & Linnoila (1990), these reports constitute one of the most highly replicated findings in biologic psychiatry.

Abnormalities in the 5-HT system have been associated with criminal offenders; specifically, reduced cerebrospinal fluid 5-HIAA concentrations have been associated with a history of violent acts and/or impulsivity in violent criminal offenders (Linnoila, Virkunen, Scheinin, Nuutila, Rimon, & Goodwin, 1983). This data suggests that a dimension of disinhibited aggression directed at others may

be associated with alterations in observed indexes of central 5-HT dysfunction.

Neuropsychological Influences on Violence

Neural Substrates of Violence

Experimental clinical studies have shown that the capacity for aggression, and for its control, is vested in a system of neuronal assemblies, both excitatory and inhibitory (Elliott, 1992). This system is believed to be situated bilaterally in the orbitofrontal cortex, hippocampus, hypothalamus, anterior lobe of the cerebellum, amygdala, dorsolateral prefrontal cortex, temporal lobe, and the basal ganglia. Under normal conditions, the neocortex also exerts some degree of control over this system, but its inhibitory capacity is fragile and can break down in the face of overwhelming endogenous drives or exogenous provocation, even in normal individuals (Elliott, 1992).

Yeudall & Flor-Henry (1975), in an extensive neuropsychological investigation of aggressive criminals, found that 76% of such subjects had dysfunction localized to the frontal and temporal regions of the brain. Of these, 79% showed fronto-temporal abnormalities lateralized to the left hemisphere. Similar localization to the dominant temporal lobe in violent adolescents has been reported by Yeudall (1978), who used this neuropsychological evidence of anterior temporal dysfunction to implicate the limbic regions of the temporal lobe, in particular, the amygdala

and hippocampus. Specific brain areas purported by Yeudall to be dysfunctional include the dorsolateral prefrontal cortex, orbitofrontal cortex, temporal cortex, basal ganglia, hypothalamus, amygdala and hippocampus.

Using CT scan, Langevin, Bain, Wortzman, Hucker, Dickey, & Wright (1988) discovered that the overall incidence of gross pathology among sexual aggressors was no different from that found in a nonsexual nonaggressive offender group. However, it should be recalled that the temporal lobes in particular have been implicated in unusual sexual behavior. When the temporal lobes specifically were examined, it was consistently found that the sexual sadists have right temporal horn dilation. Forty-one percent of the sadists showed this abnormality, compared to 11% of nonsadistic sexual aggressives and 13% of controls; these results reflect a statistically significant difference.

Kolarsky, Freund, Machek, & Polak (1967) proposed that lesions of known duration, irrespective of localization, are more frequent among sex offenders as compared to non-sex offenders. In 1982, Graber, Hartman, Coffman, Huey, & Golden examined the structural and functional integrity of the cerebrum in sexual assaulters. These investigators found impaired neuropsychological performance, decreased cerebral blood flow, and decreased brain density in a significant number of subjects.

Haugh & Markesbery (1983) suggested that the human

hypothalamus contributes to aggression. Neoplasms which bilaterally destroy the ventromedial hypothalamic area in patients have been accompanied by attacks on attendants which are strikingly reminiscent of animal aggression following ventromedial lesions. According to Weiger & Bear (1988) there are distinctive alterations in aggressive responses which result from pathology in three separate areas in the brain, suggesting that violence might result from specific lesions. Acts of violence committed by patients with ventromedial hypothalamic lesions, and by temporal lobe epileptics in the ictal or immediately postictal period, are similar in their lack of direction and complexity. An unprovoked attack might occur on whomever happened to be near the offender. An individual with a hypothalamic lesion would be likely to remember the attack while epileptics whose seizure involved the hippocampus would be amnesic for the event. The authors further explained that patients with frontal lesions tend to react in response to minor provocation and are generally incapable of planning a complex crime which involves an extended sequence of actions. This lack of planning, combined with limited foresight as to the possible consequences of their actions, would probably lead to rapid apprehension by police, though the literature does not specifically address this question. Although they remember their actions, their lack of remorse combined with difficulty in mentally

connecting the crime with the resultant punishment might lead to repeat offenses and resistance to rehabilitation.

Elliott pointed out that patients with orbitofrontal lesions show many similarities to the psychopath (Elliott, 1978). He observed that some adult psychopaths show bilateral frontotemporal theta activity on EEG which is normally present only in children. He, therefore, suggested that one cause of psychopathy might be a maturational lag in frontal lobe development.

Episodic Dyscontrol Syndrome

The term "episodic dyscontrol" corresponds to the intermittent explosive disorder described in the Diagnostic and Statistical Manual of Mental Disorders, Third Edition (American Psychiatric Association, 1987), and is viewed as a potential contributor to unpremeditated homicide, suicide, attacks on strangers, spouse battery, child abuse, criminally aggressive driving, wanton destruction of property, and savage attacks on animals (Monroe, 1978). This syndrome was first described by Kaplan (1899) as the result of severe head injuries. The "episodic dyscontrol syndrome" was named by Karl Meninger, who noted that individuals who were subject to recurrent attacks or rage in response to minor provocation often had a history of illness or injury involving the nervous system (Monroe, 1978). In patients with episodic dyscontrol, there is little warning of the drastic change in personality or of the ensuing

violence, which often has a primitive quality (e.g., gouging, kicking, clawing, and spitting). These episodic dyscontrol attacks are carried out with power and speed such that the victim may have difficulty escaping. In some cases the violence is verbal, with language becoming uncharacteristically obscene and profane.

In 102 out of 286 cases studied by Elliott (1982), the condition developed for the first time following a specific brain insult, which included severe head injury, encephalitis, stroke, brain tumor, multiple sclerosis, cerebral anoxia, or recurrent hypoglycemia. In the remaining 184 cases, the explosive behavior had been present since early life and was most commonly associated with the syndrome of minimal brain dysfunction. Other correlates were perinatal disease, persistent generalized convulsions in infancy, psychomotor epilepsy, and unexplained cerebral illnesses during early life.

Mark & Ervin (1970) describe the syndrome as involving hyperaggressivity, pathological intoxication, and impulsive sexual behavior. They suggest that this syndrome may be related to limbic system dysfunction or, more specifically, to the failure of the cortical structures of the limbic system to inhibit impulses. During interviews, sexual assaulters frequently described the rape as an impulsive behavior that sometimes occurred during an argument, or while committing another illegal act such as robbery. This

is consistent with the hypothesis that forcible sexual assault may be, in part, a result of poor judgment and poor impulse control in persons with episodic dyscontrol syndrome.

Monroe (1976) makes reference to episodic sexual disorders. He stated that when the compelling need for genital orgasm overrides appropriate postponement it becomes an episodic sexual disorder, since the sexual act becomes either personally, interpersonally, or socially destructive. He described episodic behavioral disorders as entailing: (1) a single explosive act (episodic dyscontrol); and (2) a more prolonged aberration characterized by many dyscontrol acts and other symptoms suggesting psychotic, neurotic, sociopathic, or physiologic disorders (episodic reactions).

Minimal Brain Dysfunction

The syndrome of minimal brain dysfunction (MBD) has been recognized as a common antecedent of psychopathology in adolescents and adults. Prospective and retrospective studies have confirmed that a substantial proportion of MBD children become criminals, alcoholics, hysterics, or atypical psychotics (Elliott, 1982). In many people, this was the result of a variety of anatomical defects which included vascular malformations and hamartomas, (benign tumor-like nodules composed of an overgrowth of mature cells and tissues that normally occur in the affected part, but often with one element predominating), patches of gliosis in

the cortex and white matter, ectopic groups of neurons in the white matter, and multiple patches of cortical dysplasia (Taylor, Falconer, Burton, & Corsellis, 1971). Elliott (1982) reported on 286 patients with a history of attacks of uncontrolled rage with little or no provocation, dating either from early life or following identified brain insult after the age of 15. Of these subjects, 94% showed evidence of organic disorders of the brain, whether acquired or developmental. The CT scan, though not available in the early phase of the study, disclosed abnormalities in 41 of 148 cases. The EEG, carried out with scalp electrodes and supplemented by nasopharyngeal electrodes and sleep records in some cases, was abnormal in 60.8% of 245 patients.

Attention-deficit-hyperactivity disorder (ADHD) was originally linked with specific learning disorders and a heterogeneous collection of cognitive, perceptual, motor, and behavioral disorders that constituted the minimal brain dysfunction syndrome. This complex has been subdivided into the hyperactivity disorder, the attention deficit disorder, specific learning difficulties, and minor motor disabilities. There is much overlap, however, between these components. ADHD is a common antecedent of episodic dyscontrol and other forms of antisocial conduct which may persist into adult life. It is viewed as a developmental condition that is generally chronic in nature, has a strong biologic and hereditary predisposition, and has a

significantly negative impact on the academic and social outcomes for many children (Berman, 1979). In adults with residual ADHD, global cerebral glucose metabolism is lower than in normal control subjects with significantly reduced values at 30 to 60 sites tested in the cerebrum. The multiplicity of affected areas suggest a developmental defect in a diffuse system; for instance, one involving cortical and subcortical inhibitory mechanisms (Elliott, 1992). This could help explain those cases of ADHD in which disinhibitory behavior presents in forms other than inattention and hyperactivity such as acting on impulse without "reflective delay" (Robins, 1966). Disinhibition may also appear in the form of substance abuse, excessive traffic violations, theft, and sexual offenses. This is true of many prisoners convicted of violent crimes whose histories are remarkable for episodes of impulsive antisocial behavior (Lewis & Jackson, 1985).

Left Hemisphere Dysfunction Theory

The traditional left-hemisphere dysfunction theory of violence argues for a type of structural damage to the left hemisphere that can be detected by neuropsychological tests validated against patients with known brain lesions. Deficits tend to involve functions of language (Mungus, 1988), verbal comprehension, and expressive speech (Hart, 1987).

Nachson & Denno (1987) examined the distribution of

hand, eye, and foot preferences among violent and nonviolent offenders. For these groups, there were no significant differences between right-hand preferences and right-foot preferences. However, significant group differences emerged for eye preference, with violent offenders preferring the left eye. The most frequent overall pattern for the violent offenders was right-hand and foot preferences, and left-eye preference, whereas the non-violent offenders preferred right hand, foot, and eye. The authors interpreted this pattern as indicating the existence of left-hemisphere dysfunction among violent offenders.

A more recent theory of violence proposes that violent individuals are less lateralized for speech and language processes. According to Raine & Scerbo (1991) an important advantage of the reduced lateralization theory over traditional left-hemisphere dysfunction theories is that reduced lateralization is more likely to be developmental in nature and not itself caused by violence.

Wright, Nobrega, Langevin, & Wortzman (1990) analyzed CT scans of 34 sexually aggressive men who had sexually assaulted adult females, 18 pedophiles, 12 incest offenders and 12 nonviolent non-sex offender controls. Brain area and optical density were computed for each hemisphere and for four sections within the hemispheres at the level of the temporal horns. Brain length and width was also computed, using the pineal gland as reference. From the width

measures, an index of brain symmetry was computed. Results showed that the brains of sex offenders were relatively smaller in the left hemisphere compared to controls, but there were no significant group differences in optical density. There were no subgroup differences in brain area but the segments corresponding to the left frontal and temporal areas were smaller in sex offenders than controls. There were no significant differences in brain length but sex offenders had smaller widths in both hemispheres than controls. Analysis of symmetry showed that 66.7% of pedophiles and 53.1% of sexual aggressives had asymmetric brains compared to 8.3% of incest offenders and 20.0% of controls. Pedophiles showed smaller left hemispheres than right whereas sexual aggressives were equally split between left and right asymmetry.

Antisocial Personality Disorder

This disorder connotes a particularly malign combination, (i.e., impulsivity, aggression, lack of empathy, and lack of foresight), is not uncommon after head injury or encephalitis, and occurs in a subset of the minimal brain dysfunction population. It is found at all social levels, and in gifted individuals as well as in the mildly retarded (Elliott, 1992).

A neuropathologic substrate is indicated by abnormal responses to neuropsychological tests designed to detect organicity, nonspecific electroencephalographic

abnormalities in a majority of aggressive cases, resistance to aversive condition, low levels of serotonin metabolites in the spinal fluid of adult psychopaths, and a low level of serotonin in the platelets of children with aggressive conduct disorder. Minor neurologic abnormalities are often present. In a study of 93 violent criminals, whose collective profile was that of the psychopath, 40% had EEG and/or neurologic abnormalities, including incoordination, dyspraxias, congenital stigmata, hyperactivity, hyperacousis, and photophobia (Robins, 1966).

Yeudall (1977) espoused that brain dysfunction of the frontal and temporal regions may be a necessary, but not a sufficient factor in the development of habitual criminal behaviors. In order to study forensic patients who were not psychopathic, 25 criminal patients with a diagnosis of severe personality disorder with affective features were consecutively selected from the neuropsychological files. In contrast to the psychopathic groups, they showed a greater proportion of lateralized deficits for the nondominant (right) cerebral hemisphere. 91% of the psychopaths also showed significant neuropsychological impairments, based on clinical interpretation of the test profiles. Consistent with the clinical findings were the discriminant function analyses, based on scores from the Wechsler Intelligence Scale and neuropsychological test variables, which correctly classified 88.5% of the

psychopaths. A significant finding was the localization of the dysfunction in the temporal and frontal regions of the brain, with the psychopaths showing a greater incidence of dominant (left) hemisphere dysfunction.

Neuropsychological Assessment

Scott, Cole, McKay, Folden, & Liggett (1984) administered the Luria-Nebraska Battery (LNNB) to persons who had been arrested for sexual assault. Their results were compared to those of a group of normal controls consisting of nonhospitalized volunteers, hospitalized volunteers, and hospitalized persons without histories of psychiatric and neurological disorders. The sexual assaulters performed significantly worse on 7 of the 14 scales of the battery. Subjects were then broken down into three groups: (1) those who had forcibly assaulted postpubescent victims; (2) those who had sexually molested a prepubescent child, and; (3) normal controls. A subsequent discriminant analysis survey correctly classified 68% of the subjects solely on the basis of their neuropsychological performance alone. The results of this study suggest that a large proportion of persons arrested for sexual assault may have underlying cerebral dysfunction identifiable by neuropsychological testing.

Bryant, Scott, Golden, & Tori (1984) examined the relationship between neuropsychological functioning, learning disability, and violent behavior. Subjects were

110 inmate volunteers selected from among those admitted to the California Medical Facility at Vacaville, California, and the Lincoln Regional Center at Lincoln, Nebraska. Violent subjects were defined as those with assaultive crimes against persons. A control group of nonviolent inmates had convictions for property-related offenses. The results support the contention that violent criminal offenders have serious neuropsychological deficits. Significant differences were found between the groups on all summary scales of the LNNB. These findings are in accord with the research of Spellacy (1978) and Bach y Rita, Climent, & Ervin (1978). Bryant et.al., reported that on four of the LNNB scales (Writing, Reading, Arithmetic, and Intellectual Processes), the mean scale scores of the violent group were within the pathological range. The violent group demonstrated impaired performance on tasks requiring complex integration of information from the visual, auditory, and somesthetic processing systems; the transition from sensory schemata to higher level symbolic processes; the ability to create, plan, organize, and execute goal-directed behaviors; and sustained attention and concentration.

Hucker, Langevin, Dickey, Handy, Chambers, Wright, Bain, & Wortzman (1988) utilized the LNNB, Wechsler Adult Intelligence Scale-Revised (WAIS-R), and CT scans in evaluations of 51 men charged with, or convicted of, sexual

assault on an adult female and compared these with 36 controls consisting of nonviolent, non-sex offenders. The sexual assaulters were further classified as 22 sadists and 21 non-sadists on the basis of clinical interview, criminal history and a standardized sex history questionnaire. Fifty-four percent of the sex offenders versus 16% of controls showed a significant result in an impaired direction on at least one LNNB subscale.

Langevin, Ben-Aron, Coulthard, Hessman, Ourins, Handy, Hucker, Russon, Day, Roper, Bain, Wortzman, & Weber (1985) evaluated 20 sexual aggressors who were charged with rape, attempted rape, or indecent assault. They were matched with a group of 20 nonviolent, non-sex offenders charged with theft, fraud, and possession of drugs. Significant differences were found on Speech Perception, Trails, and the Halstead Impairment Index with the sex offenders showing more impairment than the non-sex offenders. The results could not be explained on the basis of previous head injury.

Finally, Hucker, Langevin, Wortzman, Bain, Handy, Chambers, & Wright (1986) conducted a study in which heterosexual, homosexual, and bisexual pedophiles were compared to nonviolent, non-sex offenders using the Halstead Reitan Neuropsychological Test Battery. Sixty-seven percent of pedophiles showed some pathology, either on CT scan or the HRNTB, versus only 17% of controls.

The existing literature indicates that a large

proportion of persons convicted of sexual assault display some evidence of cerebral dysfunction. It is apparent, however, that not all sexual assaulters display such dysfunction. While neuropsychological functioning appears to be an important variable in understanding sexual assault, it is clearly not the only variable. One of the objectives of neuropsychological research dealing with sex offenders should be to identify individuals whose neuropsychological dysfunction places them at risk for maladaptive behavioral responses to environmental influences. Attempts to understand the ways in which individual differences in neuropsychological functioning interact with social/environmental, personality, and biological influences to increase the probability that deviant sexual acts will occur is paramount. Are specific types of offenses associated with specific patterns of neuropsychological deficit? Are offenses of the neuropsychologically impaired more likely to be violent? Can neuropsychological data assist in the classification of these subtypes? Of particular importance, can neuropsychological tests be utilized to assist in the identification of individuals who are at risk for offending in a preventive fashion? Failing this, can understanding an offender's cognitive strengths and deficits contribute to treatment planning?

The present study will investigate the following hypotheses:

(1) There is a significant difference in the neuropsychological functioning of violent sex offenders, nonviolent sex offenders, and nonviolent non-sex offenders;

(2) There is a significant difference in the neuropsychological functioning of violent non-sex offenders, nonviolent non-sex offenders, and nonviolent sex offenders.

(3) The neuropsychological functioning of violent and nonviolent sex offenders will correctly classify these two groups.

Additionally, the study will attempt to identify social/demographic variables i.e., education, race, and personality traits that may distinguish between offenders.

Method

Subjects

Four groups of adult male offenders were identified: violent sex offenders (group 1), nonviolent sex offenders (group 2), nonviolent non-sex offenders (group 3), and violent non-sex offenders (group 4). Violent sex offenses are defined in accordance with the Severity of Offense Code (DOP 823), Virginia Department of Corrections (DOC), as sexual assault, rape, sexual assault sodomy, sexual assault-carnal abuse, and sexual assault-attempted (with intent). Nonviolent sex offenses are categorized as statutory rape, sexual battery, sex offense against minor-fondling, indecent exposure, bestiality, peeping Tom, and indecent liberties (with intent to act). Nonviolent non-sex offenses include all other felonies. Violent non-sex offenses are murder, conspiracy to commit murder, homicide, conspiracy to commit homicide, kidnap, abduction, arson-endangered life, robbery-weapon, attempted robbery-weapon, malicious wounding, and unlawful wounding. A review of DOC records ensured that all participants had at least a sixth grade reading level. Offenders with a history of seizure disorder, brain tumor, hospitalization for head injury, or inpatient treatment for substance abuse were excluded from the study, as were subjects taking psychoactive medication. Additionally, nonviolent offenders with a prior conviction for a violent offense were not eligible for participation, nor were non-

sex offenders with a previous conviction for a sex offense. An effort was made to obtain a racial distribution within each group of approximately 60% black and 40% white, in order to be representative of the distribution within the state's correctional facilities. This proved impossible, as the distribution of nonviolent sex offenders within the prison system at the time of subject selection was 17% black and 74% white. Consequently, group 2 was 17% black and 83% white. The experimental group was comprised of 93 convicted felons, 25 from groups 1, 3, and 4 and 18 from group 2. The subjects ranged from 21 to 53 years of age at the time of data collection, and were incarcerated within Department of Corrections facilities.

Procedure

The proposal was presented to, and approved by both the DOC Human Research Review Committee and the Eastern Virginia Medical School Institutional Review Board. Three major institutions were selected for participation. Four hundred seventeen records were reviewed in DOC's central records office. Ninety three potential subjects and 37 alternates were selected for study. The DOC Research and Planning Unit contacted the warden at each participating prison and notified them of approval of the research project. Each warden was then contacted by the researcher and issues regarding scheduling, procedure, and accessibility to subjects were formalized. Eight examiners in addition to

the principal researcher assisted with data collection. All had a minimum of a Bachelor's degree in psychology and were trained and observed by a doctoral-level neuropsychologist before beginning data collection. The MMPI-2 was administered in group form. The remainder of the measures were administered individually. Standard procedures described in the test manuals were used.

In an effort to reduce experimenter bias effects and to ensure subject confidentiality, all researchers were "blind" to which group each subject belonged. To further ensure anonymity, upon completion of data collection names were converted into code numbers for later statistical analysis. All measures were scored by the principal researcher. Mean scores for data collected by the Neuropsychological Data Inventory (i.e., age, race, education, hand, foot, arm, and eye laterality) as well as all test scores rendered as means or percentiles, were converted into T scores, thus permitting analysis with parametric statistics.

Of the original pool of 93 subjects, one from group 1 refused to be tested because he believed that the examiners had been sent by a current Gubernatorial candidate. Four group 2 subjects refused; the reasons provided were: still currently in litigation; "too intelligent" to participate and, in two cases, disinterested due to imminent release on parole. These were replaced by inmates on the alternates list. Additionally, during the course of data collection,

39 of the original subjects were either transferred to other institutions or paroled. The DOC accommodated two subsequent visits to their central office for further file review and subject replacement. As a result, a total of seven institutions participated in the study. Among those interviewed for final selection from groups 1, 3, and 4, 23, 24, and 23, respectively, were included. One subject in group 1 was excluded due to three undocumented head injuries, all including loss of consciousness. The other was not selected as a result of stab wounds to the right hand and wrist and right and left shoulders that still caused him pain. A gunshot wound to the head at age 14 caused one subject to be eliminated from group 3. A subject from group 4, placed on Lithium and Mellaril since his incarceration to "control his anger", was also eliminated, as was one with a previously undiagnosed case of Tourette's Syndrome. All 18 of the final targeted participants in group 2 were included, resulting in an N of 88.

Of the sample of 88 subjects who participated in neuropsychological testing, 50 were accessible for testing with the MMPI-2. Of the 38 who did not report, ten were given unauthorized permission forms by the host institution, four refused, eight were paroled, two were ill, and the remaining 17 had been transferred to other facilities. Of the remaining 50, three refused to complete due to test length, four were discarded due to questionable validity

(T scores = 79-82 on Scale F,) and three due to probable invalidity (T scores = 92-122 on the F scale), resulting in an N of 41.

Measures

Demographic/Neuropsychological Data Inventory (Appendix A-1) was developed by the researcher to gather basic demographic information, to check for factors that might be indicative of neuropsychological symptomatology or history that did not manifest during the selection process, and to determine laterality. To assess hand and eye laterality, a cylinder, four inches in length and one and three-fourths inches in diameter was placed on the table in front of each subject. He was instructed to pick it up and look through it as though it was a telescope. To assess for arm and foot laterality, the subject was asked to stand, demonstrate how he would throw a baseball, then asked to demonstrate how he would kick a ball (Reitan, 1974).

The Shipley Institute of Living Scale (Shipley, 1939) (Appendix A-2) is used in clinical and research settings as a rapid screening test of current intellectual functioning. It consists of two subtests - a 40-item vocabulary test and 20-item abstraction test, each with a 10-minute time limit. The vocabulary subtest utilizes a multiple-choice format and requires the subject to select a synonym for each target word from among four possible choices. The abstraction subtest is comprised of semantic and numerical sequences

which must be analyzed and then completed by the examinee.

The Wechsler Memory Scale-Revised (WMS-R) (Wechsler, 1987 Logical Memory and Visual Reproduction (Appendix A-3) measure immediate and delayed recall of auditory-verbal and visual-graphic information, respectively. For the former, subjects are read paragraph-length stories and recall is immediately solicited. For the latter, subjects are presented with three separate cards, each displaying geometric designs that are exposed for a period of ten seconds per card. After each card is removed, the subject is asked to draw the figure as it appeared on that card. Recall (material is not re-presented) of both stories and drawings is again solicited 30 minutes later.

The Wechsler Adult Intelligence Test-Revised (WAIS-R) (Wechsler, 1981) Digit Span and Digit Symbol Subtests (Appendix A-4). Digit Span requires immediate recall of increasing lengths of digits in both forward and backwards order. It is a measure of auditory discrimination, attention, concentration, and immediate recall and is among the WAIS-R subtests more sensitive to brain dysfunction. Digit Symbol is a speeded symbol matching task of 90 seconds duration which assesses attention, concentration and visual motor coordination. It is the WAIS-R subtest that is usually most sensitive to brain dysfunction.

Controlled Oral Word Association Test (COWA) (Spreen & Benton, 1977) (Appendix A-5) is a test of verbal fluency,

consisting of three word one-minute naming trials, each of which requires the subject to say as many words as he/she can think of that begin with a given consonant.

Finger Tapping (FTDOM; FTNON (Reitan, 1969) is part of the Halstead-Reitan Neuropsychological Test Battery (HRNTB) and requires the subject to tap as rapidly as possible with each index finger on a small lever attached to a mechanical counter. The test is a measure of simple motor speed, although some degree of kinesthetic ability is necessary for successful performance.

The Trail Making Test, (Trails A; Trails B) (Reitan, 1986) (Appendix A-6) is a speeded measure of visual sequencing and mental tracking, and is a part of the HRNTB. Trails B performance has been found to be particularly vulnerable to the effects of brain dysfunction. Trails A requires the subject to draw lines to sequentially connect circles numbered from 1 to 25, which are arrayed randomly over an 8 1/2 by 11 inch sheet of paper. Trails B requires the subject to draw lines to connect 13 numbers and 12 letters in alternating sequence (i.e., from 1 to A, from A to 2, from 2 to B etc.). The test assesses visual-motor speed and coordination as well as divided attention and the ability to attend to shift set.

The Hooper Visual Organization Test (HVOT) (Hooper, 1983) (Appendix A-7) is a 30-item, motor-free measure of visual organization in which the subject is asked to name

objects from drawings of their disassembled pieces.

Minnesota Multiphasic Personality Inventory - 2 (MMPI-2), (Hathaway & McKinley, 1989) is the most recent revision of the original MMPI. It was developed to assess major personality characteristics that reflect an individual's social and personal adjustment and that can be indicative of psychological abnormality. It consists of 567 true/false items.

Results

Neuropsychological Testing

Using the three demographic variables of Age, Race, and Education, the three variables to assess laterality (hand, eye, arm, foot) and the fifteen neuropsychological test scores as the dependent measures, analyses of variance were performed with type of offense (violent sex offender, nonviolent sex offender, nonviolent non-sex offender, violent non-sex offender) as the independent measures. Table 1 presents the mean scores and standard deviations for demographic data by group; Table 2 the mean T-Scores for demographic and neuropsychological data.

Insert Tables 1 & 2 about here

There were main effects for Race, Logical Memory II (LMII), Visual Reproduction (VRI), Visual Reproduction (VRII) II, Hooper Visual Organization Test (HVOT), The Shipley Institute of Living Scale Vocabulary (SHIPVOC), The Shipley Institute of Living Scale Total (SHIPTOT), Digit Span (DIGSPAN), Digit Symbol (DIGSYM) and Finger Tapping dominant and non-dominant (FTDOM, FTNON). The results of the analysis are summarized in Appendix B-1.

Three subtests of the Wechsler Memory scale were significant. Nonviolent sex offenders scored higher than violent sex offenders and nonviolent non-sex offenders on

LMII. On VRI, violent sex offenders scored lower than all other groups. Nonviolent non-sex offenders and violent non-sex offenders were not different from each other. Nonviolent sex offenders scored higher than all other groups on VRII. There was no difference between violent sex offenders, violent non-sex offenders and nonviolent non-sex offenders. On the HVOT, violent sex offenders and non-violent non-sex offenders scored higher than nonviolent sex offenders and violent non-sex offenders.

Nonviolent sex offenders and violent non-sex offenders scored higher on SHIPVOC. Nonviolent non-sex offenders and violent sex offenders were not different from each other. SHIPTOT results revealed that nonviolent sex offenders and violent non-sex offenders scored higher than violent sex offenders and nonviolent non-sex offenders, who were not different from each other.

The two subtests of the WAIS-R served to distinguish between groups of offenders. On DIGSPAN, nonviolent sex offenders scored higher than violent sex offenders and nonviolent non-sex offenders. There was no difference between violent non-sex offenders and nonviolent non-sex offenders. Nonviolent non-sex offenders scored lower than all other groups on DIGSYM. There was no difference between the violent sex-offenders and violent non-sex offenders.

Nonviolent sex offenders and violent non-sex offenders were not different from each other on FTDOM but scored

higher than both the violent sex and nonviolent non-sex offenders. On FTNON, violent sex offenders scored lower than all other groups. Nonviolent sex offenders scored higher. There was no difference between the nonviolent non-sex offenders and violent non-sex offenders.

A General Linear Models Procedure identified Race as a factor with White subjects scoring higher on LMII, VRI, VRII, and SHIPVOC. Black subjects scored higher on the HVOT. Table 3 describes the results for grouping by Race.

Insert Table 3 about here

In an effort to identify the correlates associated with the four categories of offenders, a stepwise discriminant analysis was conducted. Twenty-two predictor variables were used; the three demographic variables, the four variables to assess laterality, and the fifteen neuropsychological test scores. For each analysis the four offender groups were used as the criterion. Using a significant F-ratio and a partial R^2 as the selection criteria, four variables emerge as significant contributors: Finger Tapping Dominant Hand (FTDOM) (0.302), Logical Memory II (LMII) (0.207), Arm Laterality (0.075), and The Trail Making Test, Part A (Trails A) (0.069). Table 4 describes the analysis.

Insert Table 4 about here

Further analysis with a Linear Discriminant Function concluded that 52.17% of violent sex offenders (group 1), 77.78% of nonviolent sex offenders (group 2), 47.83% of nonviolent non-sex offenders (group 3), and 39.13% of violent non-sex offenders (group 4) were correctly classified by the administered measures.

Personality Testing

Using three validity scales of the MMPI-2 (L,F,K) and the 10 clinical scales (HS,D,HY,PD,MF,PA,PT,SC, MA, SI) as the dependent measures, analyses of variance were performed with type of offense as the independent measures. Table five summarizes the mean scores by scale.

Insert Table 5 about here

There were main effects for Scales F and 9 (mania). The analysis is summarized in Appendix B-2. Post hoc analyses with the Student-Newman-Keuls test identified violent sex offenders and nonviolent sex offenders as different from violent non-sex offenders and nonviolent non-sex offenders and different from each other on Scale F. On scale 9 (Mania), nonviolent sex offenders were different from all other groups. Table 6 describes the results.

In an effort to identify the correlates associated with the four categories of offenders, a stepwise discriminant analysis was conducted. Thirteen predictor variables (the three validity scales and the 10 clinical scales) were entered. Using a significant F-ratio and a partial R^2 ratio as the selection criteria, Scales F (0.463) and 6 (0.435) emerge as significant contributors. The results are depicted in Table 7.

Discussion

The offenses committed by the subjects in this study involve a violation against another individual, whether it be designated as a nonviolent or violent offense. The degrees of offenses carry significantly different import, however, both to the victims and the legal system. The first purpose of the present study was to ascertain whether a difference exists between violent sex offenders, nonviolent sex offenders, and nonviolent non-sex offenders in terms of neuropsychological functioning when potential precursors of impairment are controlled. The attempt to do so was successful, as none of the groups displayed neuropsychological impairment. There were significant differences between groups, however, with group 2 (nonviolent sex offenders) scoring higher on four of the fifteen neuropsychological measures than all other groups, supporting the first hypothesis that a difference would exist between violent sex offenders, nonviolent sex offenders, and nonviolent non-sex offenders. Group 2 shared significant scores with group 4 (violent non-sex offenders), on three other measures, which was not predicted by the second hypothesis. Group 2 also differed on one demographic variable (race) and two MMPI-2 scales (F and 9). Regarding the third hypothesis, neuropsychological functioning correctly classified violent sex offenders with a percentage rate of 52.17, and nonviolent sex offenders with

a rate of 77.78.

Group 2 scored significantly higher than all other groups on VRII while group 1 scored lower on VRI, both subtests of the WMS-R. VRII is a test of delayed memory of figural material and suggests that group 2 may have a subcortical right hemisphere advantage, most likely focused in the temporal lobe (Golden, Zillmer, & Spiers, 1992). VRI measures immediate memory of figural material and is sensitive to right hemisphere damage (Berg, Franzen, & Wedding, 1987). Spatial thinking, integration of parts into wholes and spatial memory are among the tasks of this hemisphere, particularly the temporal lobe. Lower functioning in this area may result in the person experiencing difficulty in remembering visually-oriented material.

In relation to group 2, this finding is consistent with previous experimental clinical studies which have shown that the capacity for aggression and its control is housed in a system of neuronal assemblies, including the temporal lobe (Elliott, 1992). Yeudall & Flor-Henry (1975) also implicated the temporal regions of the brain with violence.

Like intelligence, memory function is not a unitary process, but represents the sum performance of many specific skills that are normally highly interrelated (Berg, 1987). In evaluating memory, one looks at several factors: the general level at which the individual functions, a

comparison of that level with other general skills such as intelligence, and additional memory skills (e.g., Digit Span). Overall, memory levels are rarely significantly better than intellectual levels, as intelligence serves as a limiting factor to memory performance. This is supported by group 2 scoring significantly higher on the vocabulary component and the total score on the Shipley, while group 1 had the lowest mean scores among the four groups.

Groups 1 and 3 scored higher than the other two groups on the HVOT. Lezak (1982) found no significant correlation with sex, education, age (with the exception of old age), or intelligence (except at borderline defective and lower levels). The face validity of the test lies in its demand on perceptual differentiation and conceptual organization (including mental rotation) of the fragmented objects. This is an interesting relationship; one might speculate that groups 1 and 3 excel in the area of conceptual organization, but this is not supported by their earning the lowest mean scores on Shipley Abstract, which also assesses conceptual organization. The Shipley, however, assesses verbal conceptual organization (Berg, et al.) while the HVOT assesses nonverbal conceptual organization. Perhaps groups 1 and 3 have learned to compensate for verbal weaknesses.

Group 2 scored significantly higher than all other groups on Digit Span, which measures immediate auditory memory or attentional capacity. Group 2's performance

suggests that they might have a left hemisphere advantage over the other three groups. Digit Span is also influenced by emotional factors such as anxiety (Golden, et al.). Results of personality testing, discussed below, suggest that group 2 experiences less psychological distress and utilizes a calmer approach to situations, which may aid in further explaining their ability to better attend to a task such as Digit Span.

To accurately interpret Finger Tapping results one must keep in mind the contralateral innervation of the motor system, and the fact that there is considerable variability in the normal population, with the preferred hand not always the faster one (Bornstein, 1985). Group 1 scored lower on FTNON than all other groups. Typically, the performances of the dominant and nondominant hands are compared, with the dominant hand usually performing about 10% better than the nondominant hand (Reitan & Wolfson, 1985). Group 1's performance should not necessarily be considered as an indication that the motor area of the contralateral hemisphere functions better, however, as they received the lowest mean score on FTDOM. Their performance may have been affected by working under time pressure when doing tests that require motor speed and kinesthetic ability. Group 2 scored higher on FTNON than all other groups, and groups 2 and 4 scored higher on FTDOM than both groups 1 and 3. It would appear that the motor areas in group 2's hemispheres

function equally well and that the motor area of group 4 subjects' contralateral hemisphere is superior.

Group 3 scored lower on Digit Symbol, than all other groups. This subtest measures a variety of factors including motor speed, attention, psychomotor efficiency, and visual-motor coordination. A deficit in attending is supported by this group's scores on Digit Span. Digit Symbol calls upon functions of the left hemisphere when dealing with symbols and on the right hemisphere for drawing shapes. Group 3's scores indicate that both left and right hemispheres functioned less effectively on this task. Additionally, group 3 may have been influenced by the time element.

Groups 2 and 4 scored higher than groups 1 and 3 on SHIPVOC and SHIPTOT. The Vocabulary subtest primarily assesses basic verbal skills. Specific factors include acquired knowledge, long-term memory, verbal comprehension, concept formation and reading ability, which reflect crystallized intelligence. The skills measured by Abstraction more closely approximate fluid intelligence tasks. In interpreting the summary scores there are four mutually exclusive possibilities. Individuals can score below average on both subtests, score average or above average on both subtests, score high on one subtest or low on the other or vice versa. The results of the present study suggest that groups 2 and 4 have better vocabulary

skills and higher general verbal intelligence than groups 1 and 3. It is certainly conceivable that the ability to contemplate and plan a crime, to consider and attempt to avoid consequences, would be skills that might be less difficult for groups 2 and 4 than groups 1 and 3.

Analysis of Variance identified race as distinguishing between group 2 and all other groups. These results should be interpreted with caution. Group 2 is not equally represented by race within this sample, as the majority of incarcerated nonviolent sex offenders are White. This phenomena generates several hypotheses. First, White males may actually engage in nonviolent sex offenses more than Black males. Secondly, nonviolent sex offenses perpetrated by White males are reported more frequently than offenses by Black males. Coincidental with this is the possibility that when nonviolent sex offenses occur within Black families, other resources (e.g., friends, clergy) are sought to resolve such problems as opposed to contacting the police and pursuing legal action.

Numerous studies have demonstrated that as early as three and four years of age, boys are cognizant of what constitutes masculine behavior (Greene, 1992). For Black men, male gender traits are augmented by racial implications. The psychohistory of Black men is replete with struggles to exercise control over their own lives (Franklin, 1992). Their historical and personal experiences

influence their perceptions of how they will be treated by society and how societal rules and codes may be applied to them. The sensitivity of many Black persons to the potential for exploitation by White persons has been referred to as cultural paranoia (Grier and Cobbs, 1968). To say that part of this paranoia has to do with the Black male's fear of how he will be treated by law enforcement officials is probably an understatement.

Faulkner (1983) uses the term "armoring" to describe behavioral and cognitive skills used by Blacks, as well as other persons of color, to decrease their psychological vulnerability in encounters with racism. Members of the Black race have used a variety of strategies to cope with racism. According to Stevenson and Rehard (1993), key domains of Black family strengths include the dependence on extended family relations, influence of a religious worldview, and family communication about surviving racism. This role of extended kinship patterns and flexibility in caretaking roles, in conjunction with cultural paranoia, could explain the underreporting of certain offenses that are considered particularly taboo.

Further analysis identified race as a factor with White subjects scoring higher on LMII, VRI, VRII, and SHIPVOC. If memory and intelligence are correlated, these results suggest that the White subjects in this study function at a higher intellectual level than the Black subjects. Black

subjects scored higher on the HVOT indicating that they may perform better on nonverbal, as opposed to verbal tasks involving conceptual organization.

Personality testing revealed that group 1 scored higher on Scale F than all other groups, and group 2 scored lower. The F scale consists of 60 items that were selected to detect unusual or atypical ways of answering the test items. The scale attempts to assess a variety of obvious and unambiguous content areas, including bizarre sensations, strange thoughts, peculiar experiences, feelings of isolation and alienation, and unlikely or contradictory beliefs, expectations, and self-descriptions (Dahlstrom, 1972). The mean score for group one was 60.444. Scores within the range of 56-64 may indicate normal persons who are slightly more conforming than usual or those who have a tendency to resort to denial mechanisms. The mean score for group two was 50.111. Scores within the range of 45-55 suggest that these individuals may be sophisticated persons who are attempting to create a favorable self-image (Greene, 1991). Elevation of the F scale provides an index of the psychological distress that the individual is experiencing and is positively correlated with the overall elevation of the entire clinical portion of the profile and particularly Scales 6 (Paranoia) and 8 (Schizophrenia). Subjects evaluated in forensic settings generally have, or perceive themselves as having, tangible gains either from

accentuating their strengths or weaknesses. In comparison to the normal population, minimization is far more common among sex offenders than exaggeration (Grossman, Haywood, & Wasyliv, 1992).

Group 2 also scored significantly lower on Scale 9 (Mania) with a mean group score of 50.333 placing them in the normal range. The remaining three groups scored in the moderate range (58-64), suggesting they tend to be more active, outgoing, and energetic but also more rebellious (Greene, 1991). External restrictions may result in agitation and overtly expressed dissatisfaction. By contrast, nonviolent sex offenders tend to be more inhibited. There is little chance of their becoming agitated and resorting to acting out behavior should they be rejected (Panton). When one considers that nonviolent offenders are usually well-known by their victims and that their relationship is established over time, it is not surprising that the nonviolent sex offenders would not display excitability or be overly sociable, as this might draw attention to their activities. Maintaining a "low profile" is tantamount to their success.

Stepwise Discriminant Analysis identified the F scale, discussed above, and Scale 6 as significant contributors. Interpersonal sensitivity, moral self-righteousness, and suspiciousness are revealed by the items that comprise this scale. The subjects participating in the present study fall

within the normal (45-57) to moderate range (58-64), suggesting a certain amount of suspiciousness and a tendency to personalize the actions of others toward them. This suspiciousness was evident in many of the interviews conducted prior to testing, but such behavior is not uncharacteristic of incarcerated felons. This population is typically elevated on other clinical scales, specifically Scale 4, often seen in conjunction with Scale 9. These individuals tend to be overactive, impulsive, irresponsible, untrustworthy, and exhibit a tendency to get into trouble (Greene, 1991). This configuration is common among those with delinquency, repeated crimes of indecent exposure (McCreary, 1975), and sex offenders (Erickson, Luxenberg, Walbek, & Seely, 1987; Hall, Mauiro, Vitaliano, & Proctor, 1986). The significance of Scale 6 may reflect a cautious approach that may be characteristic of the sample being studied, and that may have prevented additional scales from being elevated, although it does not appear to have affected the validity scales.

In summary, group 1 rendered scores significantly lower than the other three groups on two measures that are sensitive to left hemisphere impairment (SHIPVOC & SHIPTOT) and one that assesses right hemisphere impairment (VRI), suggesting a more diffuse, rather than a lateralized mode of functioning. This is supported by their scoring higher than groups 2 and 4 on the HVOT, a test not found to be

correlated to intelligence and one which performance is not affected by either right frontal or left-hemisphere lesions. Group 2 demonstrated significantly higher scores on two measures that involve left hemisphere functioning (SHIPVOC & SHIPTOT), supported by a significantly better performance on DIGSPAN, indicative of a lack of left hemisphere impairment. This group's scores on VRII suggest a right hemisphere advantage, while their performance on tests of fine motor speed (FTDOM, FTNON) indicates that both hemispheres probably function equally well. On the WAIS-R subtest that is most sensitive to cerebral damage (DIGSYM), group 3 scored lower than all other groups. They also scored lower on SHIPVOC and SHIPTOT but generally the data do not support the presence of cerebral damage. Group 4 shared significant results with group 2 on SHIPVOC & SHIPTOT which may indicate an ability to better process information with the left as opposed to the right hemisphere.

Implications for Future Research

As WAIS-R Digits Forward and Digits Backward do not involve identical operations, further analysis that examines them as separate scores as opposed to a combined total score is suggested.

The issue of race as a variable in terms of group distribution is perplexing. It is possible that the hypotheses generated above in reference to group 2 being significantly more populated by white subjects are correct.

An alternative may be how systems react to offenders based upon race. A survey tapping several institutions (e.g., the courts, social services, schools) may shed some light on this situation.

Harris & Lingoes (1955) developed three subscales within Scale six: Persecutory Ideas, Poignancy, and Naivete; and four subscales within Scale 9: Amoralilty, Psychomotor Acceleration, Imperturbability, and Ego Inflation. Evaluation of the data with these subscales might provide further insight regarding differences among the four groups.

While the "cycle of violence" hypothesis supports the notion that abused and neglected children have a higher likelihood of subsequent criminal behavior (Widom, 1989; Koss & Dinero, 1988), the antecedents of violent crime may include childhood victimization, head injuries, and alcohol and drug abuse. A longitudinal study focusing on documented cases of all of the above variables is indicated.

Legitimization of violence theory suggests that most victims of crime are known to their perpetrators. Determining the nature of the relationships in future studies of this type would assist in shedding additional light on the finding herein. Additionally, Brown & Strauss (1988) reported that legitimate violence is more prevalent in states that have a disproportionate number of divorced and single men. Marital status was not included in the

demographic data that was collected for this research but should be considered in future studies.

Finally, this project was originally designed to include adolescent sex offenders. While it is widely accepted that "most" sex offenders were sexually abused as juveniles, little attention has been paid to the study of adult offenders with juvenile histories as perpetrators. To surmise that sexual assault through the life span does not exist is naive. Future research should address this issue. Additionally, the propensity to be involved in situations that might result in head injury (e.g., motor vehicle accidents) as well as indulging in substance abuse is usually often higher during late adolescence. Evaluation of offenders between the ages of 12 and 18 would assist in determining if there are neuropsychological differences that exist beyond the scope of what has been presented in the research thus far.

Implications for Treatment

Sex offenders are unique in that they have committed a crime, but may be perceived as requiring treatment as opposed to incarceration. Courts often order a sex offender into treatment without evaluation by a mental health professional. Thus, sex offenders presenting for treatment may be in active denial and very poorly motivated to engage, or progress, in treatment. They may participate due to the extrinsic motivation of a prison sentence that has been

suspended or the possibility of parole, but the intrinsic motivation to actually engage with the treatment program is often lacking.

Treating sex offenders in a prison environment is fraught with pros and cons. While the therapist has a captive audience, and need not be concerned about canceled appointments, this group has already been adjudicated, convicted, and incarcerated. It is often difficult for inmates to become invested in therapy when it doesn't provide an option to their not going to prison or ensure their parole. Theoretically, the ideal intervention involves support from family members. It is often difficult for the therapist treating sex offenders in a prison setting to meet with the offender's family given the traveling time required to visit many prison facilities. This is compounded by the likelihood of many offenders being members of dysfunctional families who have no interest in a family approach to rehabilitation. Abused and neglected children have a higher likelihood of arrest for delinquency, adult criminality, and violent criminal behavior (Widom, 1989). According to Schroeder (1989), criminal behavior is most commonly concentrated in inner-city areas where the family structure is most greatly fragmented. In a study released in 1988 by the Department of Justice, researchers found that of the juveniles in state-operated institutions in 1987, only about 30% had lived with both parents while growing up.

Fifty-four percent had lived in single-parent household, while another 16% lived with grandparents or in some other arrangement without both parents.

The topography of sex offenders indicates that most violent offenders range in age from adolescence through early thirties and usually begin their criminal careers at the lower end of the age spectrum. They usually have a varied criminal background, including such crimes as break and enter, theft, and physical assault (Baxter, D.J., Marshall, W.L., Barbaree, H.E., Davidson, P.R., & Malcom, P.B., 1984). According to the authors, violent sex offenders have been classified in a variety of ways, most of which focus on the primary motivations for raping, but seem to fall within one of the following categories. For one group, the sexual offense results from poor impulse control, and the offense is one of many instances of unsocialized behaviors with the perpetrator being indifferent to the trauma experienced by their victims. The second group is comprised of the pervasively angry rapist who often inflicts serious victim injury. Their anger is generalized, independent of sexual arousal or motivation and not restricted to women. A third group is comprised of rapists whose anger is focused exclusively on women. Their assaults are characterized by verbal abuse and physical violence, usually result in harm, and often the degradation and humiliation of the victim.

Nonviolent sex offenders are more likely to be older than rapists. They do not demonstrate the same diversity of nonsexual offenses in their criminal history and they are not likely to have begun their criminal career as early as the violent sex offenders (Baxter, et al). Nonviolent sex offenders tend to fall into one of two categories: interpersonal or narcissistic. Interpersonal contact indicates that the relationship between the offender and victim occurs over a broad range of activities, not restricted to sexual interactions, and that the primary goal of sexual contact is not necessarily orgasm. Narcissistic contact is primarily sexual and directed toward orgasm (Knight, R.A. & Prentky, R.A., 1990).

The goals of a program designed to successfully treat sex offenders should include the offender assuming full responsibility for the sexually abusive behavior, acquiring insight regarding the behavioral patterns that led to the crime and, perhaps most importantly, decreasing recidivism. This study indicates that there is a difference between violent and nonviolent sex offenders. Hopefully, this finding can help the therapist think strategically about intervention. For example, violent sex offenders' scores on SHIPVOC and SHIPTOT are indicative of lower left hemisphere functioning; their performance on VRI suggests lower right hemisphere functioning. Higher HVOT scores support the notion that neither the left nor right

hemisphere dominates. Treatment modalities that focus on verbal skills and behavior change through education will probably not be successful with this group. Based upon test results, behavioral techniques are recommended.

Assertiveness training can be useful in treating violent sex offenders who may lack skills to express both positive and negative feelings and to differentiate between aggression and assertiveness. These deficits make it difficult for them to establish and maintain a social relationship which might lead to an appropriate bond with another individual. Primary aspects of assertiveness training include expressing one's ideas more clearly, reducing anger, and controlling impulsive behavior. Employing techniques such as modeling, graded task assignments, and role playing, ideally with videotaped feedback, are behavioral methods that might be successful with this group. A group setting can be particularly useful for assertiveness training.

Internal locus of control, operationally defined as one's experience of who/what has control over his life, is another useful technique with violent sex offenders. They attempt to restructure their own experiences of their ability to make choices and positively control aspects of their lives. These proactive choices become part of their experiential storage reservoir. As they become more personally powerful, the ego strength required to examine

their crimes and assume responsibility develops. Social skills training, behavioral rehearsal, and relaxation exercises are other techniques that might prove beneficial.

Sex education is an important aspect of any offender treatment program. For this group, emphasis should be placed on commonly held sexual myths, including the pattern of sexual arousal and appropriate sexual communication. To accomplish this, listening to sexually arousing tapes until satiation occurs and arousal decreases has been used in some settings.

Nonviolent sex offenders scored higher on SHIPVOC, SHIPTOT, and DIGSPAN, functions of the left hemisphere. Their performance on VRI suggests a right hemisphere advantage. Higher scores on FTDOM and FTNON support both hemispheres functioning well, although the left hemisphere seems to be slightly superior to the right. Because they seem to be somewhat higher functioning, a cognitively oriented approach is recommended for this group.

The approach used in Cognitive Therapy has been described as "collaborative empiricism" (Beck, Rush, Shaw, & Emery, 1979). The therapist attempts to assist the individual in helping him or her recognize the cognitions and other factors that cause problems, to test the validity of the thoughts, beliefs, and assumptions that prove important, and to make the needed changes in cognition.

The majority of these individuals have offended in a

manner that is particularly insensitive to the morals and ethics of our society. When there is a discrepancy between that which has been done and society's belief about appropriate behavior, dissonance is created which leads to considerable anxiety, guilt, and depression. To avoid these emotions, most offenders develop cognitive distortions that support their continued involvement in deviant sexual activities, therefore, cognitive restructuring is recommended as the first phase. This element of treatment is designed to explore the validity of each perpetrator's cognitive beliefs that justify the violation. It is realized that this phase of treatment is extremely difficult, for it is this super structure of distorted beliefs that allowed the offender to engage in his behavior. Guided Association/Guided Discovery and thought stopping are two additional techniques appropriate for this group.

Given the nature of many of the nonviolent offenses, empathy is included as a phase. The offender attempts to acquire sufficient insight to facilitate understanding the feelings, thoughts, and trauma their victim(s) experienced as a result of the abuse. The victims participating in the treatment process is especially salient if he or she is a family member.

Sex education is also a component for the nonviolent sex offenders with emphasis on what is accepted as normal sexual behavior and where each offender fits along that

continuum. Sexual dysfunctions should also be addressed.

Relapse prevention techniques are applicable to both groups. The goal is to ensure that the offenders have assimilated the information provided and possess the skills for utilizing the information to prevent re-offending. Specific areas of weakness should be targeted on an individual basis and a determination is made regarding each offender's "readiness" for discharge from the program.

The question of the uniqueness of sexual offenders as compared to other criminals and of the need for special statutes and programs for sexual offenders have been prominent in forensic settings. The results of the present study support the concept that violent sex offenders differ from nonviolent sex offenders in terms of neuropsychological functioning; violent sex offenders utilize a diffuse rather than a lateralized mode of processing information and nonviolent sex offenders have a slight left hemisphere advantage and are somewhat higher functioning. Differences between the two groups were also found on two of the MMPI-2 scales and, combined with the neuropsychological data, suggest that violent and nonviolent sex offenders represent two distinct clinical groups.

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Table 1Demographic Data by Group

Group	<u>1 (n=23)</u>	<u>2 (n=18)</u>	<u>3 (n=24)</u>	<u>4 (n=23)</u>
Age				
Mean	32.000	34.111	29.292	32.217
SD	7.230	8.123	6.231	7.754
Education				
Mean	11.565	12.722	12.292	11.913
SD	1.534	1.745	2.350	1.857
% by Race				
Black	60.870	16.667	58.333	60.870
White	39.130	83.333	41.667	39.130

Table 2Mean T-Scores for Demographic and Neuropsychological Data
by Group

Group	<u>1 (n=23)</u>	<u>2 (n=18)</u>	<u>3 (n=24)</u>	<u>4 (n=23)</u>
Age (yrs.)	50.300	49.822	50.092	49.117
Education (yrs.)	50.617	50.023	50.683	54.696
Race	52.674	50.775	49.833	52.391
Laterality				
Hand	52.243	56.222	49.488	49.452
Foot	49.452	49.700	49.488	49.422
Arm	49.452	49.700	49.488	49.452
Eye	48.948	47.600	49.725	52.922
LMII	41.304	48.167	42.458	46.478
VRI	46.391	52.389	48.333	50.304
VRII	46.391	53.889	46.750	48.609
HVOT	50.870	46.611	51.833	47.174
SHIPVOC	39.391	49.389	41.542	43.696
DIGSYM	42.348	48.944	40.500	44.522
LMI	43.391	46.333	42.583	46.905
SHIPABS	46.696	52.824	48.870	50.957
SHIPTOT	42.304	51.588	44.870	49.478
TRAILS A	45.391	43.222	44.652	47.783

(table continues)

TRAILS B	47.217	47.667	43.826	47.130
FTDOM	39.174	51.833	40.522	46.696
FTNON	43.043	51.778	44.826	47.913
DIGSPAN	41.565	52.056	44.957	48.000
COWA	49.000	52.333	48.458	52.909

Table 3Grouping by Race

<u>Variable</u>	<u>5=Black</u>	<u>6=White</u>	<u>Race</u>
	<u>Mean</u>	<u>N</u>	
LMII	45.909	44	6
	42.841	44	5
VRI	50.591	44	6
	46.614	44	5
HOOPER	51.136	44	5
	47.455	44	6
SHIPVOC	48.295	44	6
	38.000	44	5
DIGSYM	44.591	44	6
	42.932	44	5

Table 4

Stepwise Discriminant Analysis Summary for
Neuropsychological Variables

Variable Entered	<u>FTDOM</u>	<u>LMII</u>	<u>HAND</u>	<u>TRAILS A</u>
Partial R**2	0.302	0.207	0.075	0.689
F Statistic	11.101	6.597	2.038	1.825
Pr>F	.000	.000	.116	.150
Wilks' Lambda	.698	.554	.512	.477
Pr<Lambda	.000	.000	.000	.000
Average Squared	.101	.150	.166	.179
Canonical Corr.				
Pr>ASCC	.000	.000	.000	.000

Table 5MMPI-2 Mean T-Scores for Dependent Variables

Scales

L	55.097
F	55.170
K	48.390
HS	51.341
D	51.463
HY	48.512
PD	62.243
MF	48.097
PA	54.219
PT	52.121
SC	55.024
MA	58.609
SI	49.365

Table 6Student-Newman-Keuls Grouping for Scales F & 9

<u>Variable</u>		<u>Group</u>	<u>Mean</u>	<u>N</u>
Scale F	A	1	60.444	9
	A			
	B A	3	56.692	13
	B A			
	B A	4	53.000	10
	B			
	B	2	50.111	9
Scale 9	A	1	62.222	9
	A			
	A	3	61.462	13
	A			
	B A	4	59.100	10
	B			
	B	2	50.333	9

Table 7Stepwise Discriminant Analysis Summary for MMPI-2

Variable Entered	<u>MA</u>	<u>PA</u>	<u>F</u>	
Variable Removed				<u>MA</u>
Partial R**2	0.192	0.120	0.148	0.129
F Statistic	2.293	2.993	2.027	1.725
Pr>F	0.463	0.435	0.128	0.180
Wilk's Lambda	0.808	0.647	0.551	0.632
Pr<Lambda	0.046	0.132	0.010	0.009
Average Squared	0.064	0.127	0.167	0.134
Canonical Corr.				
Pr>ASCC	0.463	0.013	0.013	0.009

Appendix A

Measures

Examiner:
Name:
Location:
D.O.B.:
Education:

Date:
Code:
Race:
Age:
Handedness:

1. Do you...

- ☐ wear glasses
☐ wear contact lenses

Examiner's Comments

Have you had...
☐ blurred vision
☐ double vision

2. Test for peripheral vision...

1. ☐ 2. ☐ 3. ☐

3. Do you have...

- ☐ decreased hearing in the
left ear
☐ decreased hearing in the
right ear
☐ decreased hearing in both
ears

4. Do you have...

- ☐ pain or numbness in your right
fingers, hand, or arm
☐ pain or numbness in your left
fingers, hand, or arm

5. Do you have...

- ☐ pain
☐ headaches

6. Have you had...

- ☐ black-out spells
☐ fits or seizures

7. Have you had...

- ☐ head injuries
☐ a stroke
☐ a brain tumor
☐ treatment for substance abuse
☐ injury to the hands or arms

8. Do you...

- ☐ drink alcohol
If yes, how much?
☐ Use street drugs...
If yes, which ones?

- take prescribed or over-the-counter medications
If yes, which ones?
- work with chemicals
If yes, which ones?

9. Test for laterality...
- L/R kick a ball
 - L/R throw a ball
 - L/R telescope

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Appendix B
Analyses of Variance

Analysis of Variance

SOURCE	SS	df	MS	F	Pr>F
<u>Age</u>					
MODEL	251.850	3	83.950	1.37	0.259
ERROR	5164.649	84	61.483		
<u>Race</u>					
MODEL	2.536	3	0.845		
ERROR	19.463	84	0.231	3.65*	0.015
<u>Education</u>					
MODEL	15.225	3	5.075	1.08	0.363
ERROR	396.047	84	4.714		
<u>Hand Laterality</u>					
MODEL	0.475	3	0.158	.07	0.528
ERROR	17.888	84	0.212		
<u>Foot Laterality</u>					
MODEL	1.765	3	0.588	1.18	0.324
ERROR	42.053	84	0.500		
<u>Arm Laterality</u>					
MODEL	0.712	3	0.237	1.80	0.152
ERROR	11.059	84	0.131		

(table continues)

Source	<u>SS</u>	<u>df</u>	<u>MS</u>	<u>F</u>	<u>Pr>F</u>
<u>Eye Laterality</u>					
MODEL	43.852	3	14.617	0.83	0.480
ERROR	1478.511	84	17.601		
<u>LMII</u>					
SOURCE	<u>SS</u>	<u>df</u>	<u>MS</u>	<u>F</u>	<u>PR>F</u>
MODEL	665.557	3	221.852	4.95*	0.003
ERROR	3763.067	84	44.798		
<u>VRI</u>					
MODEL	569.513	3	189.837	3.50*	0.019
ERROR	4555.350	84	54.230		
<u>VRII</u>					
MODEL	697.845	3	232.615	3.70*	0.148
ERROR	5277.234	84	62.824		
<u>HVOT</u>					
MODEL	444.794	3	148.264	5.27*	0.148
ERROR	2363.524	84	28.137		
<u>SHIPVOC</u>					
MODEL	1094.495	3	364.831	3.27*	0.002
ERROR	9360.583	84	111.435		

(table continues)

Source	<u>SS</u>	<u>df</u>	<u>MS</u>	<u>F</u>	<u>Pr>f</u>
<u>DIGIT SYMBOL</u>					
MODEL	798.087	3	266.029	2.68*	0.521
ERROR	8339.900	84	99.284		
<u>LMI</u>					
MODEL	296.704	3	98.901	1.76	0.161
ERROR	4609.121	82	56.208		
<u>SHIPABS</u>					
MODEL	425.187	3	141.729	1.80	0.152
ERROR	6438.905	82	78.523		
<u>SHIPTOT</u>					
MODEL	1105.037	3	368.345	5.19*	0.002
ERROR	5819.335	84	70.967		
<u>Trails A</u>					
MODEL	228.762	3	76.254	0.63	0.595
ERROR	9991.719	83	120.382		
<u>Trails B</u>					
MODEL	208.886	3	69.628	0.58	0.629
ERROR	9943.826	83	119.805		
<u>FTDOM</u>					
MODEL	2083.931	3	694.643	7.76*	0.000
ERROR	7426.413	83	89.474		

(table continues)

Source	<u>SS</u>	<u>df</u>	<u>FTNON MS</u>	<u>F</u>	<u>Pr>F</u>
MODEL	885.514	3	295.171	3.13*	0.030
ERROR	7835.198	83	94.399		
<u>DIGSPAN</u>					
MODEL	1219.780	3	406.593	5.70*	0.001
ERROR	5919.553	83	71.319		
<u>COWA</u>					
MODEL	339.901	3	113.300	1.75	0.162
ERROR	5367.776	83	64.672		

MMPI-2 Analysis of Variance

<u>Source</u>	<u>SS</u>	<u>df</u>	<u>MS</u>	<u>F</u>	<u>PP>F</u>
<u>L</u>					
Model	41.431	3	13.810	0.12	0.948
Error	4308.177	37	116.437		
<u>F</u>					
Model	557.924	3	185.974	2.64*	0.063
Error	2607.880	37	70.483		
<u>K</u>					
Model	176.948	3	58.982	0.57	0.635
Error	3796.807	37	102.616		
<u>HS</u>					
Model	61.871	3	20.628	0.15	0.926
Error	4939.347	37	133.495		
<u>D</u>					
Model	91.408	3	30.469	0.35	0.790
Error	3224.786	37	87.156		
<u>HY</u>					
Model	35.235	3	11.745	0.09	0.963
Error	4603.008	37	124.405		

(table continues)

Source	<u>SS</u>	<u>df</u>	<u>MS</u>	<u>F</u>	<u>PR>F</u>
<u>PD</u>					
Model	204.182	3	68.060	0.77	0.516
Error	3255.378	37	87.983		
<u>ME</u>					
Model	101.654	3	33.884	0.37	0.773
Error	3361.955	37	90.863		
<u>PA</u>					
Model	1021.847	3	340.615	2.45	0.079
Error	5153.176	37	139.279		
<u>PT</u>					
Model	3392.792	3	68.199	0.74	0.533
Error	204.597	37	91.724		
<u>SC</u>					
Model	309.464	3	103.155	1.21	0.317
Error	3141.511	37	84.906		
<u>MA</u>					
Model	842.069	3	280.689	2.93*	0.046
Error	3545.686	37	95.829		
<u>SI</u>					
Model	304.103	3	101.367	1.13	0.350
Error	3323.408	37	89.821		

Pamela Knox-Jones was born in New York City, New York and raised in Teaneck, New Jersey. She attended Howard University, majoring in anthropology, before moving to the Tidewater area. She completed requirements for a bachelor's degree in Special Education at Norfolk State University in 1976 and a master's degree in psychology at Old Dominion University in 1982. She taught mentally retarded and learning disabled students in the Norfolk School system from 1976-1984. She was the Chief Psychologist at St. Bride's Correctional Center in Chesapeake, Virginia from 1984-1989, at which time she accepted the position of Court Psychologist, Hampton Juvenile and Domestic Relations Court, Hampton, Virginia. She maintained this position until 1991 when she pursued studies at the Virginia Consortium for Professional Psychology. She is the Past President of the Virginia Association of Correctional Psychologists, and the Current Membership Chair of the Virginia Applied Psychology Association. She was the recipient of a Letter of Commendation from the Norfolk Public Schools (1977); a University Fellowship, Old Dominion University (1982) and the Black American Research Assistantship, Old Dominion University, 1991. She was also appointed to The Promising Administrator's Corp, Virginia Department of Corrections, (1986).

Time-Frequency Analysis of Increases in Vaginal Blood Perfusion Elicited by Long-Duration Pudendal Neuromodulation in Anesthetized Rats

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Objectives: Female sexual dysfunction (FSD) affects a significant portion of the population. Although treatment options for FSD are limited, neuromodulation for bladder dysfunction has improved sexual function in some women. A few studies have investigated peripheral neuromodulation for eliciting changes in vaginal blood flow, as a proxy for modulating genital sexual arousal, however results are generally transient. Our central hypothesis is that repeated or extended-duration pudendal nerve stimulation can elicit maintained vaginal blood flow increases.

Materials and Methods: Under ketamine anesthesia, the pudendal nerve of 14 female rats was stimulated at varying frequencies (1–100 Hz) and durations (0.15–60 min). Vaginal blood perfusion was measured with a laser Doppler flowmetry probe. Changes in blood perfusion were determined through raw signal analysis and increases in the energy of neurogenic (0.076–0.200 Hz) and myogenic (0.200–0.740 Hz) frequency bands through wavelet analysis. Additionally, a convolution model was developed for a carry-over stimulation effect.

Results: Each experiment had significant increases in vaginal blood perfusion due to pudendal nerve stimulation. In addition, there were large concurrent increases in neurogenic and myogenic frequency-band energy in 11/14 experiments, with an average maximal response at 31.3 min after stimulation initiation. An effective stimulation model with a 30-min carry-over effect had a stronger correlation to blood perfusion than the stimulation period itself.

Conclusions: Repeated or extended-duration pudendal nerve stimulation can elicit maintained increases in vaginal blood perfusion. This work indicates the potential for pudendal neuromodulation as a method for increasing genital arousal as a potential treatment for FSD.

Keywords: blood flow, internal organ function, peripheral nerve stimulation, pudendal nerve stimulation, sexual function

Conflict of Interest: The authors reported no conflict of interest.

INTRODUCTION

Female sexual dysfunction (FSD) is a widespread medical problem that may affect up to 45% of women (1,2). FSD has several subtypes, which may be concurrent (3). Female orgasmic disorder is characterized by rare or absent orgasm (10–42% prevalence). Female sexual interest or arousal disorder (FSIAD) is characterized by significantly reduced psychological sexual interest, lack of physical arousal, pleasure, or both. Genito-pelvic pain or penetration disorder is characterized by vulvovaginal or pelvic pain due to intercourse or penetration (15% prevalence). In contrast to male sexual arousal, the physical and psychological aspects of female sexual arousal are highly dependent on one another. Flibanserin is a recent FDA-approved drug that exclusively treats FSIAD (4). Currently, there are no effective treatment options specifically targeting the genital, rather than psychological, component of female sexual arousal (5). In part, this is due to the challenge of studying the mechanisms of the physiological components of female arousal, an area of research that is still developing (6). A treatment for genital arousal dysfunction may also

affect other components of sexual dysfunction, and thus would have wide applicability across FSD subtypes.

Sildenafil, FDA-approved for male erectile dysfunction, has been shown to improve FSD symptoms in some women with sexual arousal disorder, including improvements in sensation, lubrication,

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and orgasm (7). Studies with sildenafil in women have correlated increases in clitoral and vaginal blood flow to improvements in sexual function (8,9). However, sildenafil administered to women has a high likelihood of moderate adverse events, most commonly headaches (7), and has had unclear clinical benefits due to conflicting reports of efficacy (10,11). An optimal treatment would result in consistent improvements in sexual function while minimizing adverse events.

Preliminary studies in women have indicated a potential for spinal and peripheral neural stimulation to improve sexual functioning. The pudendal nerve innervates the pelvic region, including the vagina, labia, and clitoris (12), and plays an important role in physiological sexual arousal (13). Sacral neuromodulation (SNM), in which stimulation is applied to spinal roots that include the pudendal nerve, has gained acceptance as a treatment option for bladder or bowel dysfunction (14). A few studies have shown that some women treated with SNM for overactive bladder also have an improvement in sexual function (15–17), which were not correlated with improvements in bladder function (17). While these studies indicate the promising potential of sexual neuromodulation, there has not been a thorough analysis of the mechanisms and effects of stimulation.

Vaginal blood perfusion can be used as a proxy for physiological sexual arousal as increased vaginal blood flow is associated with genital arousal (18–20). Laser Doppler flowmetry (LDF) is a noninvasive method for measuring microvascular blood perfusion, and has been used to assess vaginal blood perfusion in rodent studies (18–23). Raw LDF measurements have several limitations, including non-absolute values and a high sensitivity to motion artifacts. A time-frequency analysis method has been developed for various uses of LDF, that aims to mitigate these limitations (24,25). Microvascular perfusion exhibits oscillations in activity based on underlying metabolic, neurogenic, and myogenic activity, as well as oscillations associated with respiration and heart rate (24–26). The neurogenic oscillatory range of LDF is associated with sympathetically driven changes in microvascular perfusion (27). Several studies have indicated that increased sympathetic drive leads to increased genital arousal in women (28–31). Since the pudendal nerve carries sensory inputs to autonomic spinal circuits associated with arousal, we expect that pudendal nerve stimulation will have a similar effect as direct sympathetic stimulation of arousal circuits. Thus, we hypothesized that there would be increases in the neurogenic range of intravaginal LDF measurements due to pudendal nerve stimulation. In addition, the myogenic frequency range, associated with increased vascular diameter due to a rise in blood pressure, may also increase as the vaginal tissue becomes engorged.

This study specifically examines the potential for neuromodulation via pudendal nerve stimulation to increase vaginal blood perfusion, a preliminary step in the development of a neuromodulation treatment for FSD. While some rat studies have shown that peripheral nerve stimulation, including short-duration pudendal nerve stimulation, can cause transient changes in vaginal blood flow (18,21–23), none have shown a sustained arousal response lasting minutes or longer. In this study with anesthetized rats, we used raw LDF and time-frequency analyses to assess vaginal blood perfusion changes induced by up to 30 min of stimulation, and developed a simple stimulation-carryover model.

MATERIALS AND METHODS

All procedures were approved by the University of Michigan Institutional Animal Care and Use Committee, in accordance with

the National Institutes of Health's guidelines for the care and use of laboratory animals. Female, mature, nulliparous Sprague-Dawley rats ($n = 18$; animals 1–4: Envigo, Haslett, MI, USA; animals 5–18: Charles River Breeding Labs, Wilmington, MA, USA) weighing between 210 and 330 g (261.1 ± 33.4 g) were used. Anesthesia was induced prior to surgery by isoflurane (4–5%) followed by a ketamine/xylazine/acepromazine (90 mg/kg, 7.5 mg/kg, 1.5 mg/kg, respectively) intraperitoneal cocktail. Since the rat estrous stage is known to have a significant effect on rat sexual receptivity (32), a vaginal lavage was performed after induction of anesthesia prior to surgery in order to determine the estrous stage. Anesthesia during surgery and experimentation was maintained with ketamine (30 mg/kg every 30 min; intraperitoneal), as it has been used in related studies examining sexual arousal-related responses (23,33,34). Four experiments did not result in data collection due to surgery or electrode failure, resulting in 14 animals for data collection.

The left pudendal nerve was exposed via a posterior approach. Platinum-wire hook electrodes were secured to the nerve ($n = 5$) with silicone elastomer (Kwik-Cast, World Precision Instruments, Sarasota, FL, USA) or lab-made nerve cuffs (1-mm inner diameter silastic tubing, AS636 wire, Cooner Wire, Chatsworth, CA, USA) were placed around the nerve ($n = 9$). Stimulation was performed with varying frequencies (1–100 Hz) and amplitudes (0.5–3 V) with an isolated pulse stimulator (Model 2100, AM Systems, Carlsborg, WA, USA). Most stimulation periods used 10 Hz (applied in 13/14 experiments; previously shown to activate sympathetic pathways to pelvic organs [35]) and 2 V stimulation, which was $\sim 2\times$ the motor threshold for an anal twitch. Stimulation was current controlled in the first two experiments (156.9 ± 130.5 μA mean amplitude) and voltage-controlled stimulation in the remaining experiments (2.38 ± 0.95 V). The entire pudendal nerve (motor and sensory branches) was stimulated, as to better replicate the nonspecific stimulation delivered in clinical SNM.

A LDF pencil probe (MNP110XP, ADInstruments, Colorado Springs, CO, USA) was inserted 1–2 cm into the vagina and angled against the anterior wall. Vaginal blood perfusion with the LDF probe was measured with a Blood FlowMeter (50 Hz sampling rate, model INL191, ADInstruments), which measures blood perfusion on a scale of 0–5000 blood perfusion units (BPU). A Grapevine Neural Interface Processor (Ripple, Salt Lake City, UT, USA) and desktop PC were used as a data acquisition system, with a custom MATLAB (Mathworks, Natick, MA, USA) interface created for real-time data viewing. Recordings were paused for maintenance anesthesia dosing or other animal adjustments that may have introduced motion artifacts into the blood perfusion signals. The vaginal lumen diameter (VLD) was measured with digital calipers at two time points in the last six experiments; before any stimulation was applied and at the end of the experiment after LDF recordings were completed. After completion of all experimental procedures, animals were euthanized with an intraperitoneal injection of euthasol (sodium pentobarbital, 300–400 mg/kg).

Two types of pudendal nerve stimulation experiments were performed. The first set of experiments ($n = 6$) were short-stimulation duration experiments. In these experiments, multiple stimulation periods (0.17–5.00 min, 0.97 ± 0.64 min) were delivered sequentially with short inter-trial breaks. Blood perfusion was measured before any stimulation was delivered (0.60 – 2.32 min, 0.99 ± 0.68 min), during stimulation (26.62 – 114.37 min; 55.73 ± 30.80 min, including time between stimulation periods), and after stimulation (1.09 – 3.04 min; 1.64 ± 0.78 min). The results of short-stimulation duration experiments indicated that stimulation had a cumulative effect. A second

set of experiments ($n = 8$) used long-stimulation durations. In these experiments, long continuous stimulation periods (4.98–57.68 min, 27.53 ± 11.25 min) were used. Again, blood perfusion was measured before (1.11–5.95 min; 2.74 ± 1.94 min), during (31.12–141.15 min; 92.54 ± 33.47 min, including time between sequential long-stimulation periods), and after (5.23–27.65 min; 15.64 ± 9.90 min) stimulation. Baseline periods are defined as the time before the start of the first stimulation.

All data were analyzed in MATLAB. Sequential stimulation recording periods in one experiment were combined into one data file for analysis. We assumed that changes in LDF signals during brief non-recording periods between data files, that is, for ketamine re-dosing, were negligible. LDF baseline levels between trials and animals sometimes varied based on slight differences in probe position, so the minimum value of each trial was set to zero prior to any data file combination. Stimulation intervals with strong, efferent-driven muscle contractions, characterized by at least a 100% increase in blood perfusion within 1 sec of stimulation onset, were not included in data analysis as they were assumed to be direct activation of pelvic floor muscles. In order to maintain consistent analysis between experiments, the time between trials was considered negligible.

LDF signals were also analyzed using time-frequency representations (TFRs), with a continuous wavelet transform (CWT) method (24,25) in MATLAB. Blood perfusion signals were segmented into two key frequency domains: neurogenic (0.076–0.200 Hz), and myogenic (0.200–0.740 Hz), as previously established by Humeau and colleagues (24,25). The scalogram energy (in arbitrary units) was calculated for each frequency range, to convert to a single continuous parameter in time (36). Scalogram energy is typically used as a relative measurement. As we were primarily interested in changes in scalogram energy throughout the experiment, we determined the percent change in each energy range as compared to the baseline period.

While there is no established threshold for sexual arousal in the framework of changes in vaginal blood flow, we sought to quantify the timing and duration of large changes in vaginal perfusion. We identified a combined threshold that was sufficiently effective at separating periods of inactivity from periods with notable changes in vaginal blood flow dynamics by visual inspection of a subset of experiments. The vaginal blood flow threshold (VBFT) is defined by simultaneous increases in raw LDF blood perfusion (100% increase), neurogenic energy (500% increase), and myogenic energy (500% increase) as compared to the corresponding mean baseline levels for each.

Our results suggested that vaginal blood flow responses are not directly correlated with the onset and offset of pudendal nerve stimulation, but rather with an accumulation of applied stimulation over time. Thus, we investigated the potential relationship between vaginal blood perfusion and pudendal stimulation based on a cumulative amount of stimulation delivered. In order to assess potential time dependency of changes in vaginal blood perfusion to the applied stimulation, we assessed the distribution of data points that exceeded the VBFT over time. As discussed in the Results, the peak probability of the VBFT being exceeded was at 31.3 min after stimulation started followed by a decay to baseline. For the analysis here, we rounded this time parameter to 30 min. Using this information, we investigated two potential models of stimulation accumulation and duration of effect (s_{eff} , Eq. (1)), in addition to a direct relationship to the applied stimulation (s_{app} , Eq. (2)). For the s_{eff} of the first model (Model 1), we convolved s_{app} with an exponential function ($w_{\text{Model-1}}$, Eq. (3) where t is time in seconds), which has an empirically determined decay constant λ (Eq. (4)). For the s_{eff} of the second model

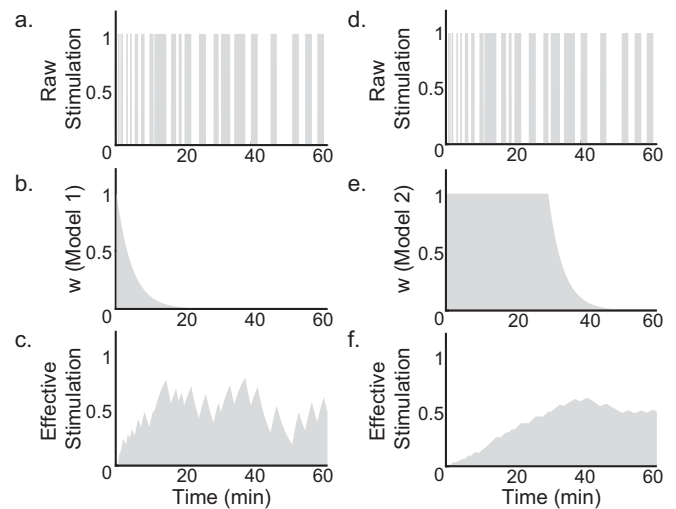


Figure 1. Models of effective stimulation for a repeated short-duration stimulation experiment (Experiment 5). a,d. Applied stimulation s_{app} for Experiment 5. b. Model 1 convolution function $w_{\text{Model-1}}$. c. Corresponding $s_{\text{eff-1}}$. e. Model 2 convolution function $w_{\text{Model-2}}$. f. Corresponding $s_{\text{eff-2}}$.

(Model 2), we convolved s_{app} with a function ($w_{\text{Model-2}}$, Eq. (4)) that is constant for 30 min and then decays with λ .

$$s_{\text{eff}} = w * s_{\text{app}} \quad (1)$$

$$s_{\text{app}} = \begin{cases} 0, & \text{stimulation off} \\ 1, & \text{stimulation on} \end{cases} \quad (2)$$

$$w_{\text{Model-1}} = e^{-\lambda t} \quad (3)$$

$$\lambda = \frac{\log 0.001}{1800} \quad (4)$$

$$w_{\text{Model-2}} = \begin{cases} 1, & t \leq 1800 \text{ sec} \\ e^{-\lambda(t-1800)}, & t > 1800 \text{ sec} \end{cases} \quad (5)$$

For each model, s_{eff} was separately normalized across experiments so that the maximum stimulation equaled one. Each model resulted in a unique effective stimulation curve, as shown in Figure 1 for a repeated short-duration stimulation experiment.

In order to determine if there was a significant change in vaginal blood flow from baseline, we performed a t -test (unpaired samples, unequal variance) between the LDF blood perfusion, neurogenic energy, and myogenic energy data sets for before and after the first stimulation period in each experiment. A Bonferroni correction was used to account for multiple comparisons. A significant difference was characterized by $\alpha < 0.01$ ($n = 3$, $p < 0.003$ with Bonferroni correction). A one-way ANOVA was performed to determine if estrous state had a significant effect on the total time above VBFT for each experiment. To quantify the relationship between stimulation and the changes in vaginal blood flow in each experiment, we performed a linear regression between each stimulation curve (s_{app} , $s_{\text{eff-1}}$, $s_{\text{eff-2}}$) and each test variable (blood perfusion, percent change in neurogenic energy, percent change in myogenic energy). The relationship between neurogenic and myogenic energy was also investigated with a linear regression. The linear correlation coefficient r -value and corresponding p -value were determined for each linear regression. The linear regressions were considered significant

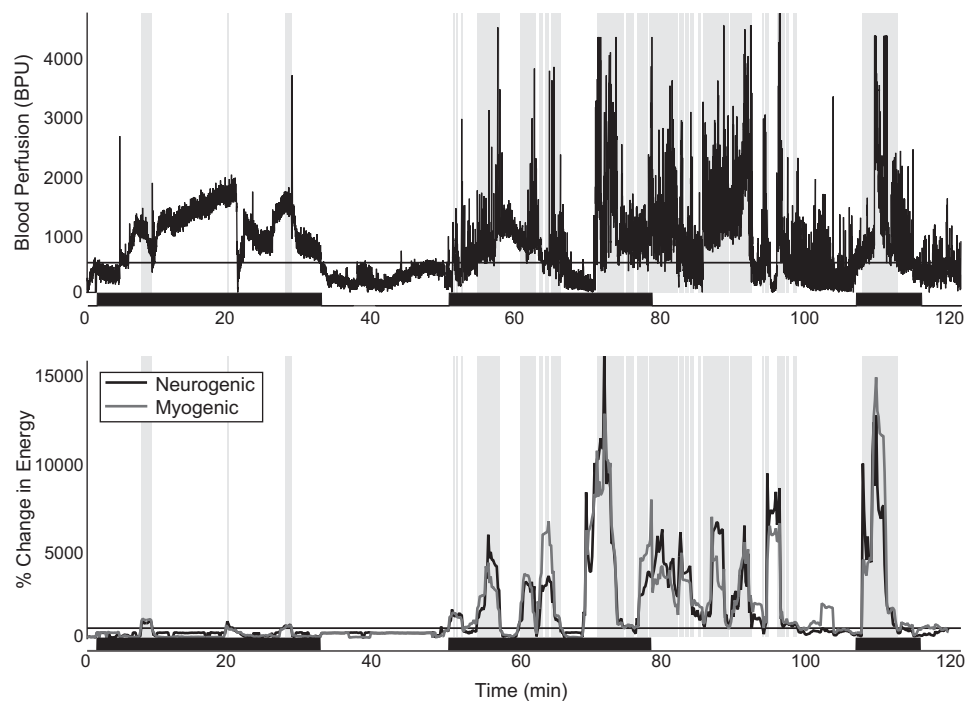


Figure 2. Example long-duration pudendal stimulation experiment showing increases in vaginal blood perfusion (Experiment 8). a. Vaginal blood perfusion. The horizontal line indicates the threshold for a 100% increase in raw blood perfusion from the baseline period. b. Percent change in neurogenic and myogenic energy. The horizontal line indicates a 500% increase in energy from the baseline period for both energy bands. Stimulation intervals (10 Hz) are indicated by black bars above the x-axis. Regions with gray background indicate when the VBFT was exceeded.

if $p < 0.01$. Presented values are given as mean $\pm$ standard deviation, when appropriate.

RESULTS

Most rats ($n = 12$) had significant increases in raw LDF blood perfusion as compared to the baseline period ($p < 0.003$). Increases in blood perfusion were frequently accompanied with increases in neurogenic and myogenic energy. Across experiments, neurogenic and myogenic energy were strongly correlated ($r = 0.79 \pm 0.13$, $p < 0.01$ for all experiments). Figure 2 shows blood perfusion and the corresponding time-frequency analysis in an example experiment. Only rarely were the entire neurogenic and myogenic energy values significantly greater ($p < 0.003$) than baseline for the duration of an experiment ($n = 1$ for each neurogenic and myogenic). However, 11 of 14 experiments crossed the VBFT (Fig. 3). The average total duration above VBFT was 11.7 ± 11.7 min across all 14 experiments

(14.9 ± 11.2 min for 11 experiments that exceeded VBFT). All raw and analyzed data sets, as well as MATLAB analysis code, are accessible online (37).

The increases in vaginal blood perfusion were not directly related to the onset of stimulation (except in cases of efferent muscle activation that were omitted from analysis), but rather exhibited a delayed or cumulative response. Figure 4 shows the distribution of time points across all experiments that were above VBFT. The peak probability of response was at 31.3 min after stimulation started, for analyzed trials. Subsequent peaks in the distribution are due to additional stimulation sequences throughout some experiments (e.g., Fig. 2). We used this information to inform our stimulation models, as described above. Model 1 assumes that the effect of stimulation decays exponentially over 30 min. Model 2 assumes that the effect of stimulation is constant for 30 min, and then decays exponentially over 30 min. Figure 4 also gives distribution fits for experiment data split by stimulation duration or stimulus frequency. Each data division had a peak probability of response

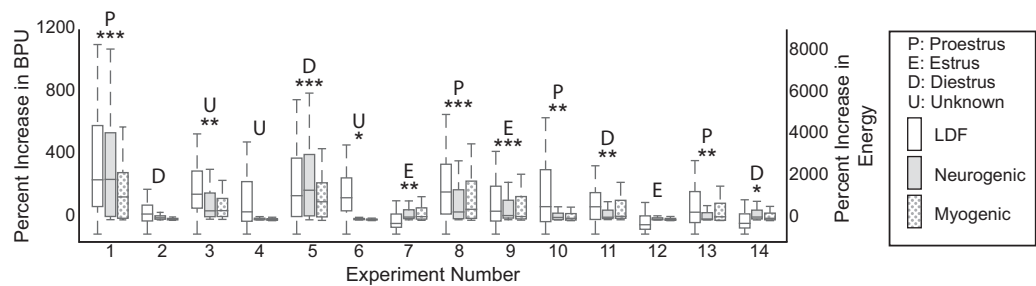


Figure 3. Distribution of vaginal blood perfusion changes across experiments. Box plots for percent increases in blood perfusion (left axis) and neurogenic energy and myogenic energy (right axis) for each experiment. *VBFT-time < 5 min, **VBFT-time 5–10 min, ***VBFT-time > 10 min.

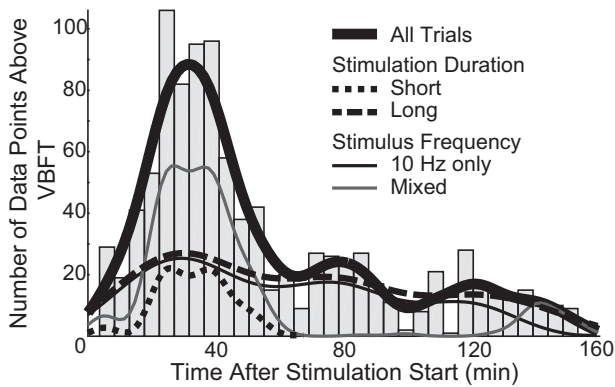


Figure 4. Distribution of experimental time points crossing VBFT across all experiments. The superimposed curve ("All Trials") is a non-parametric kernel-smoothing distribution, which provides a fit to histogram data with multiple peaks. This curve-fit yields a maximum at 31.3 min, with a strong fit to the data ($r^2 = 0.911$, $p < 0.001$). Distribution-fit curves are also given for two separate data divisions. Dashed curves represent separate fits to short-stimulation duration experiments ($n = 6$; peak at 25.7 min) and long-stimulation duration experiments ($n = 8$; peak at 30.9 min). Thin, solid curves represent fits to experiments with only 10 Hz used ($n = 6$; peak at 29.6 min) and experiments in which the applied stimulation frequencies were mixed ($n = 8$; peak at 26.4 min).

within 25–30 min after stimulation initiation. The 10 Hz only experiments are six of the eight long-duration stimulation experiments, leading to a strong relationship between the two curves.

Through our analysis of effective stimulation, we generally observed stronger correlations between the vaginal responses and $s_{\text{eff-1}}$ or $s_{\text{eff-2}}$ rather than s_{app} . Figures 5 and 6 show effective stimulation models for example short-duration and long-duration stimulation experiments, as well as the linear regression fit between each stimulation curve and the test variables. We found that in many experiments ($n = 4$ short-duration; $n = 4$ long-duration), blood perfusion was most positively correlated with Model 2 ($r = 0.33 \pm 0.13$).

Blood perfusion for two long-duration experiments was most positively correlated ($r = 0.34, 0.36$) with Model 1 and for four experiments ($n = 2$ short-duration; $n = 2$ long-duration) was most positively correlated ($r = 0.25 \pm 0.17$) with s_{app} . For all experiments, the correlations between blood perfusion and each of the three models were significant ($p < 0.01$). The percent increase in neurogenic energy was most likely to be positively correlated ($r = 0.34 \pm 0.27$) with Model 2 ($n = 6$ short-duration; $n = 5$ long-duration). The percent increase in neurogenic energy in one ($n = 1$) long-duration experiment was most positively correlated ($r = 0.24$) with Model 1 and, in two long-duration experiments ($n = 2$), was most positively correlated ($r = 0.12, 0.29$) with s_{app} . All correlations between percent increase in neurogenic energy and the most highly correlated model were significant ($p < 0.01$). The percent increase in myogenic energy was also most likely to be positively correlated ($r = 0.35 \pm 0.22$) with Model 2 ($n = 5$ short-duration; $n = 5$ long-duration). For all of these experiments, the correlation with Model 2 was significant ($p < 0.01$). The percent increase in myogenic energy in two ($n = 2$) long-duration experiments was most positively correlated ($r = 0.07, 0.26$) with Model 1; one experiment was significantly correlated with Model 1 ($p < 0.01$) and one experiment showed a trend toward a correlation with Model 1 ($p = 0.06$). The percent increase in myogenic energy in two experiments ($n = 1$ short-duration; $n = 1$ long-duration) was most positively correlated ($r = -0.12, 0.29$) with s_{app} ; one experiment was significantly correlated with the raw stimulation curve ($p < 0.01$) and one experiment showed a trend toward a correlation ($p = 0.11$). Since neurogenic and myogenic energy were strongly correlated, the correlation coefficients between each model and neurogenic/myogenic energy were similar. In 11 experiments, neurogenic and myogenic energy were most positively correlated with the same model. In the experiments where the most positively correlated model differed between neurogenic and myogenic energy, the most positive correlations with the models were relatively weak ($r = 0.03 \pm 0.15$ for correlations with neurogenic energy, $r = 0.02 \pm 0.12$ for correlations with myogenic energy).

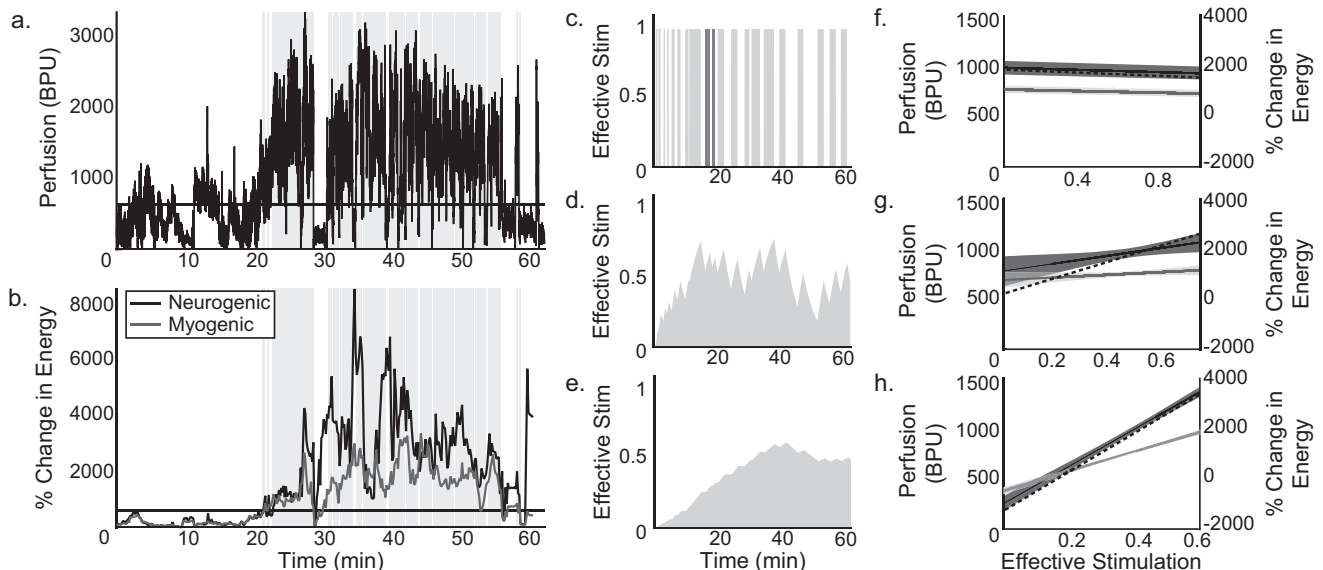


Figure 5. Effective stimulation analysis for repeated short-stimulation experiment (Experiment 5; 10 and 20 Hz stimulation). a. Blood perfusion. Horizontal line indicates 100% increase in perfusion compared to baseline. VBFT crossed in shaded regions. b. Percent change in neurogenic (black) and myogenic energy (gray). Horizontal line indicates 500% increase in energy for both energy bands. VBFT crossed in shaded regions. c–e. Effective stimulation curves (normalized to one, unitless) for no stimulation transformation (c), Model 1 (d), and Model 2 (e). Each stimulation interval was 10 Hz except for two 20 Hz intervals (dark gray). f–h. Linear regression between blood perfusion (black) or percent change in energy (neurogenic = dark gray, myogenic = light gray) and effective stimulation model indicated in (c–e). Shaded regions indicate 95% confidence intervals on each mean value distribution.

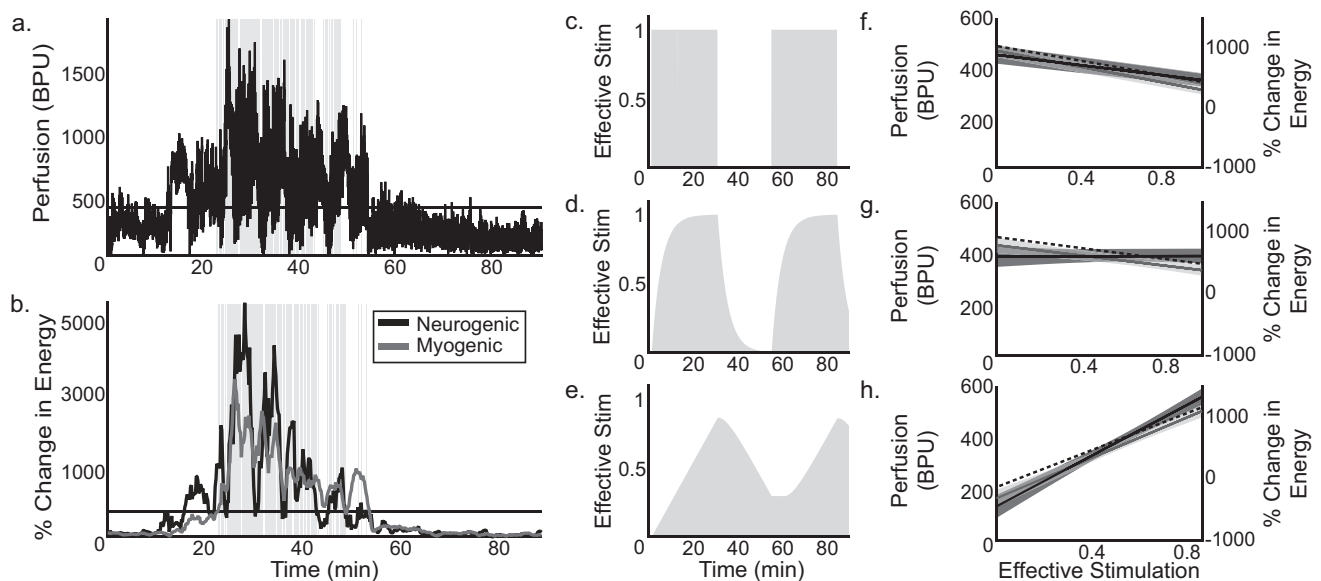


Figure 6. Effective stimulation analysis for long-stimulation experiment (Experiment 9; 10 Hz stimulation). Figure subparts as in Figure 5.

Four experiments occurred during the proestrus phase, three experiments occurred during the estrus phase, and four experiments occurred during the diestrus phase (Fig. 3). The remaining experiments had poor or unclear lavage samples. When comparing the total time that each experiment was above VBFT, experiments conducted during proestrus, diestrus, and estrus were not statistically different ($F(2,8)=1.44$, $p=0.29$). However, there was a trend toward proestrus having the longest time above threshold (25.08 ± 20.84 min) compared to estrus (10.10 ± 10.49 min) and diestrus (17.05 ± 21.71 min). In the six experiments where VLD was measured, there was a mean increase in lumen diameter across the stimulation period of $50.8 \pm 52.0\%$. Five of six experiments had an increase in diameter, with only Experiment 11 decreasing (-5.1%). Across all experiments, we did not visually observe any pelvic floor contractions.

DISCUSSION

In these experiments, we demonstrated that repeated or extended-duration electrical stimulation on the pudendal nerve can lead to increases in vaginal blood perfusion, both in the raw LDF signal and the low-frequency signal content within neurogenic and myogenic frequency bands (Figs. 2, 5, and 6). Although this was not a consistent response, a majority of our experiments (79%) had large concurrent increases in the raw LDF signal as well as TFRs in the two frequency bands (Fig. 3). There was often a strong relationship between neurogenic and myogenic energy, which indicates a general increase in low-frequency oscillations in blood perfusion due to pudendal nerve stimulation. As blood flow changes can be related to sympathetic-mediated contractions of smooth muscle in blood vessel walls (24), this relationship is expected. The concurrent crossing of three LDF signal parameters (raw signal increase, neurogenic frequency band increase, myogenic frequency band increase) is a potential novel approach for detecting maximal blood flow changes. Interestingly, on average across experiments, most VBFT crossings occurred about 20–40 min after stimulation initiation (Fig. 4).

The results of our study indicate that there was a cumulative effect of stimulation, which eventually fades (Figs. 4–6). In our

convolution model we estimated that stimulation has an effect for up to one hour, but that the effect of stimulation decays starting at approximately 30 min. This estimation of stimulation effect generally described the results more accurately than assuming there was a direct response to single stimulation periods or that the stimulation automatically decays. A cumulative stimulation effect may indicate increased activation of spinal circuits over time or is necessary to overcome descending inhibition (13). Increased sympathetic activity due to arousal may also result in a positive feedback loop, which would increase the effective duration of stimulation. While a mechanism for sexual arousal involving sympathetic and parasympathetic feedback has been proposed, the dynamics are not well-understood (38). Our observed blood flow responses are much longer in duration than rat coitus. Similarly, the continuous stimulation applied by SNM does not relate to intercourse duration. It is possible that the benefits of neuromodulation for FSD include an improvement in genital organ blood flow and an increased ability to become aroused. Further preclinical and clinical studies are needed to investigate these relationships.

To our knowledge, this is the first work to evaluate the effect of long-duration (up to 30 min) pudendal nerve stimulation on vaginal blood perfusion. Prior studies evaluating pudendal (18) and pelvic nerve stimulation (21–23) for changes in vaginal blood flow used stimulation durations within 5–30 sec, with further examination focused on neural pathways (18) or the impact of various pharmacological interventions (23). The observed blood flow responses in these studies were generally on the same time-duration order of magnitude (~ 15 sec to 2 min in duration) as the applied stimulation. In those experiments, it is possible that pelvic floor contractions were occurring, with blood flow responses mirroring somatic muscle contraction. In our studies, the large blood perfusion responses that lasted for 5–10 min or longer show a longer-time course in the response, providing further support to autonomic nervous system modulation. In Cai et al., their 20-sec pudendal nerve stimulation trials generally had LDF signal increases that were delayed after stimulation cessation (18), possibly obtaining a shorter response version of the results in our study. Our additional observation of increased VLD after stimulation, in five of six measured animals, suggests that

the pelvic floor was not contracting for the duration of our applied stimulation. A future study including analyses of blood flow changes in other pelvic structures, such as the rectum, might indicate if our observed response is a local or multi-organ response. Interestingly, our use of (up to) 30-min stimulation periods is similar to stimulation session durations of percutaneous tibial nerve stimulation (PTNS) for bladder function, which has also had benefits for some women with FSD (39). Future work should also investigate this alternative pathway.

Our use of TFRs to provide additional analyses of LDF responses mitigates against signal contamination due to artifacts. For example, the LDF signal drift during the first stimulation period in Figure 2 was likely due to a slow settling of the LDF probe position. TFR analysis removed this artifact, and ultimately large perfusion changes were observed in the experiment. Prior nerve stimulation work generally focused on the raw LDF signal (18,21–23), and thus artifacts may have contaminated their observations. Breathing and bladder contractions can lead to signal confounds (23), however the typical rate of those activities are outside our specific frequency ranges of interest. Under anesthesia, our rats had breathing rates within 44–120 breaths per minute, which aligns with a frequency range previously reported (0.74–2 Hz) (24,25). Bladder contractions under ketamine anesthesia while saline is also being infused have been reported at rates within 0.012–0.076 contractions per second (40–42), below our neurogenic frequency range. One study which utilized TFRs in rat vaginal blood flow analyses evaluated combined frequency responses in a 0.013–0.6 Hz low-frequency range and a 0.6–2.5 Hz high-frequency range (19) without accounting for possible bladder or respiration contamination. Although we did not record bladder pressure in this work, our use of TFRs specifically in the neurogenic and myogenic ranges should have mitigated against their effect on our data.

The probability and timing of a LDF response to stimulation varied across experiments (e.g., Figs. 2, 5, and 6). Studies investigating peripheral nerve stimulation for similar autonomic applications like bladder control, also have also reported inconsistent responses to the repeated stimulation parameters across experiments (35,43), as did a prior study assessing short pudendal nerve stimulation for changes in vaginal blood perfusion (18). There are several potential explanations for these variations. Experiments were performed during the day, when rats are typically less active and thus handling may have caused stress. The anesthetic depth may have changed within or across animals, particularly as urethane is known to be a better anesthetic agent for studies of pelvic organ function than ketamine (40,44). While we attempted to be consistent in LDF probe placement, the relative position may have varied within or across experiments. We did not perform a wide stimulation parameter evaluation, although our primary use of 10 and 20 Hz stimulation frequencies align with prior work that obtained maximal responses for these patterns in comparison to others (22,23). It is also possible that surgical exposure and electrode placement may have led to nerve damage, though nerve functionality was confirmed at the start with observation of anal twitch responses. Additionally, there is the normal presence of noise in the nervous system (45), which in our case may be accentuated by involving sensory, spinal, and motor pathways. Even with these potential factors, the large blood perfusion increases in a majority of experiments provide support for pudendal nerve stimulation for driving neural circuits that affect vaginal blood flow. Future studies will investigate the specific nerve pathways and spinal circuits involved in these responses.

Another potential cause of variation between animals is the estrous cycle. Female rats' hormones are determined by the estrous

cycle, which is analogous to the human menstrual cycle. However, rat sexual receptivity is strongly affected by estrous stage. There are three main phases of the rat estrous cycle: proestrus, estrus, and diestrus. The estrus phase is generally considered sexually receptive stage, but recent studies have shown that sexual receptivity also occurs during proestrus and that sexual receptivity is low during the daylight hours of estrus (46). Our results did not have a significant dependence on the estrous phase, which could indicate two possibilities. First, this could indicate that hormone levels do not affect genital arousal driven by the peripheral nervous system. Second, this could indicate that pudendal nerve stimulation is able to offset differences in baseline receptivity. The latter case could indicate the potential for pudendal nerve stimulation to offset low arousal and provide a treatment for aspects of FSD. A post hoc power analysis of our results ($p = 0.09$) revealed that a larger scale study ($n \approx 160$) would be necessary to better determine the relationship between estrous phase and response to stimulation. In addition to larger scale studies, future work will include the use of ovariectomized and hormone-primed rats (47) to further investigate the impact of estrous cycle on pudendal nerve stimulation-driven vaginal arousal.

As the stimulation pattern and parameters are important in activation of autonomic pathways for organ control (35,43), further studies need to be conducted to determine the optimal stimulation paradigm to increase neurogenic vaginal blood perfusion oscillations. Due to variations in stimulation duration and some alternating of stimulus frequencies during short-stimulation duration experiments, a balanced, comprehensive statistical comparison of stimulation patterns was not possible for the experiments performed here. Qualitatively, across experiments there were no relationships to applied stimulation frequency or amplitude. Although 10 Hz only experiments had a different distribution of points above the VBFT than experiments with mixed frequencies (Fig. 4), 10 Hz was also used in all but one of the mixed-frequency experiments. It is possible that variations in the stimulus pattern (43), as was used to some extent in the mixed-frequency experiments, may lead to a greater excitation. We plan to perform a more rigorous evaluation of the stimulation parameter space in future work. The methods presented in this paper may be used for such a study to provide valuable quantitative analysis.

CONCLUSIONS

This study provides further insight into electrical stimulation of peripheral nerves for eliciting changes in vaginal blood flow. Our use of repeated and long-duration stimuli are closer in relevance to stimulation applied with SNM and PTNS than prior short-duration stimulation studies. Clinical improvements in sexual function for women with SNM may be due, at least in part, to neural-mediated processes leading to changes such as increases in vaginal blood flow. A detailed analysis of both the physiological effects of stimulation as well as the dynamics of the response to stimulation will help to inform future work toward the development of neuromodulation treatments for FSD.

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Authorship Statements

All authors contributed to designing the study. Ms. Rice, Ms. Zimmerman, Dr. Ross, and Dr. Bruns performed the experiments. Ms. Rice, Ms. Zimmerman, Dr. Berger, and Dr. Bruns reviewed and analyzed the data. Ms. Rice and Dr. Bruns drafted the manuscript. All authors reviewed the final manuscript.

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COMMENTS

The authors are trying to examine the scientific underpinnings of the occasional report of improved sexual function in women undergoing neuromodulation. To that end they performed “long-term” stimulation of the pudendal nerve in rats and measured blood perfusion in the vagina. They demonstrated increased perfusion with their hypothesized may be related to changes in sexual function in women.

Howard Goldman, MD
Cleveland, OH, USA

The authors presented an animal model where the electric stimulation of the pudendal nerve increased the vaginal blood flow in female rats.

I believe that the methodology adopted in such an experiment is flawed for the following reasons:

1. The description of the changes in the blood flow has not been determined in other areas (dermatomes) supplied by the pudendal nerve. If one to be assertive that the pudendal nerve is involved in this study, the authors should have registered the changes of the blood flow in other areas such as the rectum supplied by the pudendal nerve.
2. It would have been a stronger study if the authors had included oophorectomized rats and those with hormonal addition to find out

what is the mechanism of pudendal stimulation involved in the vaginal blood flow. The current manuscript does not add any potential clinical use of their technique in addressing the problem with female sexual dysfunction.

3. There is no mention of the amplitude of pudendal stimulation and how this could be translated into the clinical application. The experiment should have been performed in the awoken state to quantify the threshold of stimulation tolerated by the animal and if this amplitude is enough to elicit blood flow changes.

Magdy Hassouna, MD, PhD
Toronto, Ontario, Canada

Comments not included in the Early View version of this paper.

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Peer reviewed

Arousal regulates frequency tuning in primary auditory cortex

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Edited by Eric I. Knudsen, Stanford University School of Medicine, Stanford, CA, and approved October 30, 2019 (received for review July 2, 2019)

Changes in arousal influence cortical sensory representations, but the synaptic mechanisms underlying arousal-dependent modulation of cortical processing are unclear. Here, we use 2-photon Ca^{2+} imaging in the auditory cortex of awake mice to show that heightened arousal, as indexed by pupil diameter, broadens frequency-tuned activity of layer 2/3 (L2/3) pyramidal cells. Sensory representations are less sparse, and the tuning of nearby cells more similar when arousal increases. Despite the reduction in selectivity, frequency discrimination by cell ensembles improves due to a decrease in shared trial-to-trial variability. In vivo whole-cell recordings reveal that mechanisms contributing to the effects of arousal on sensory representations include state-dependent modulation of membrane potential dynamics, spontaneous firing, and tone-evoked synaptic potentials. Surprisingly, changes in short-latency tone-evoked excitatory input cannot explain the effects of arousal on the broadness of frequency-tuned output. However, we show that arousal strongly modulates a slow tone-evoked suppression of recurrent excitation underlying lateral inhibition [H. K. Kato, S. K. Asinof, J. S. Isaacson, *Neuron*, 95, 412–423, (2017)]. This arousal-dependent “network suppression” gates the duration of tone-evoked responses and regulates the broadness of frequency tuning. Thus, arousal can shape tuning via modulation of indirect changes in recurrent network activity.

brain state | inhibition stabilized network | lateral inhibition | signal correlation | noise correlation

Information processing in the sensory cortex is modulated by changes in behavioral states such as those associated with arousal, attention, or task engagement (1–4). Indeed, moment-to-moment changes in arousal have strong effects on spontaneous and stimulus-evoked firing activity in the primary visual (V1) (5–12) and auditory (A1) cortex (13–15). Despite the potential for arousal to regulate cortical sensory coding, the subthreshold synaptic mechanisms by which changes in brain state influence sensory representations and tuning properties are not well understood.

In recordings from head-fixed mice, changes in arousal are typically assessed by measurements of pupil diameter or exploratory behavior, such as locomotion, with increases in pupil diameter and bouts of running/walking indicating heightened arousal (1). Interestingly, the transition from quiet wakefulness to locomotion has different effects in the visual and auditory cortices: walking/running increases stimulus-driven firing in V1 (5, 6, 8, 10, 16) while it is associated with a decrease in sensory-evoked firing in A1 (13–15). However, heightened arousal does not require movement, and recent work suggests that motor feedback signals to the sensory cortex modulate activity differently than arousal tracked by pupillometry during quiet wakefulness (5, 13).

In this study, we use pupillometry and Ca^{2+} imaging to study how fluctuations in arousal in the absence of locomotion modulate frequency coding in A1 of head-fixed mice. We show that, despite a reduction in frequency selectivity, elevated arousal improves frequency discrimination by L2/3 pyramidal cells. In vivo whole-cell current- and voltage-clamp recordings from L2/3 cells reveal how changes in membrane potential dynamics and tone-evoked synaptic input contribute to this arousal-dependent modulation of frequency representations.

Results

We used transgenic mice expressing the Ca^{2+} indicator GCaMP6s [Emx-Cre;CamKII-tTA;Ai94(TITL-GCaMP6s)] (17) and 2-photon imaging (950 nm) to study tone responses in A1 L2/3 pyramidal cells ($n = 8$ imaging fields, 5 mice). Prior to recording, head-fixed mice were habituated to sitting quietly for prolonged time periods (1 to 2 h) on a static platform. During imaging of A1 in the right hemisphere, mice sat on a passive treadmill that measured movement while an IR camera simultaneously monitored the pupil (illuminated by IR laser emission through the eye) of the contralateral eye and blocks of pure tones (17 log spaced frequencies, 2–40 kHz, 1 s duration, 3 s ITI, 60 dB) were delivered to the contralateral ear (Fig. 1A). During single imaging sessions, pupil diameter (normalized to maximum pupil diameter) fluctuated between constricted and dilated states (Fig. 1B). Under our conditions, mice were predominantly stationary, and while sporadic locomotion bouts were associated with maximally dilated pupils, mice spent considerable time with pupils just as dilated while stationary (Fig. 1B and C). For all experiments ($n = 8$), we excluded the small number of trials during locomotion and, thus, limited our investigation to how arousal (indexed by pupil diameter) modulated cortical activity.

We examined the influence of arousal by sorting tone trials by the mean pupil diameter during the tone. While responses were rarely observed when pupils were most constricted (1–20% of maximal diameter), the same tones elicited robust responses as pupil diameter increased (Fig. 1D). This reflects the fact that both the amplitude and the reliability of tone-evoked responses were strongly dependent on arousal. At best frequency ([BF], the frequency eliciting the strongest response in each cell averaged across all pupil diameters unless stated otherwise), the response amplitude and trial-to-trial reliability increased more than 4-fold (Friedman’s ANOVA, $P < 0.001$) when pupils were most dilated [81–100% vs. 1–20% maximal diameter (Fig. 1E)]. These

Significance

Changes in brain state modulate how information is processed in sensory cortical areas. Here we use population imaging and intracellular recording to show that arousal regulates frequency tuning in layer 2/3 of primary auditory cortex. Increased arousal reduces lateral inhibition, broadens frequency tuning and enhances cortical representations of pure tones. Despite the arousal-dependent reduction in stimulus selectivity, frequency discrimination by cell ensembles improves due to a reduction in correlated variability (noise correlations).

Author contributions: P.-A.L., S.K.A., N.J.E., and J.S.I. designed research; P.-A.L., S.K.A., and N.J.E. performed research; P.-A.L., S.K.A., N.J.E., and J.S.I. analyzed data; and P.-A.L., S.K.A., and J.S.I. wrote the paper.

The authors declare no competing interest.

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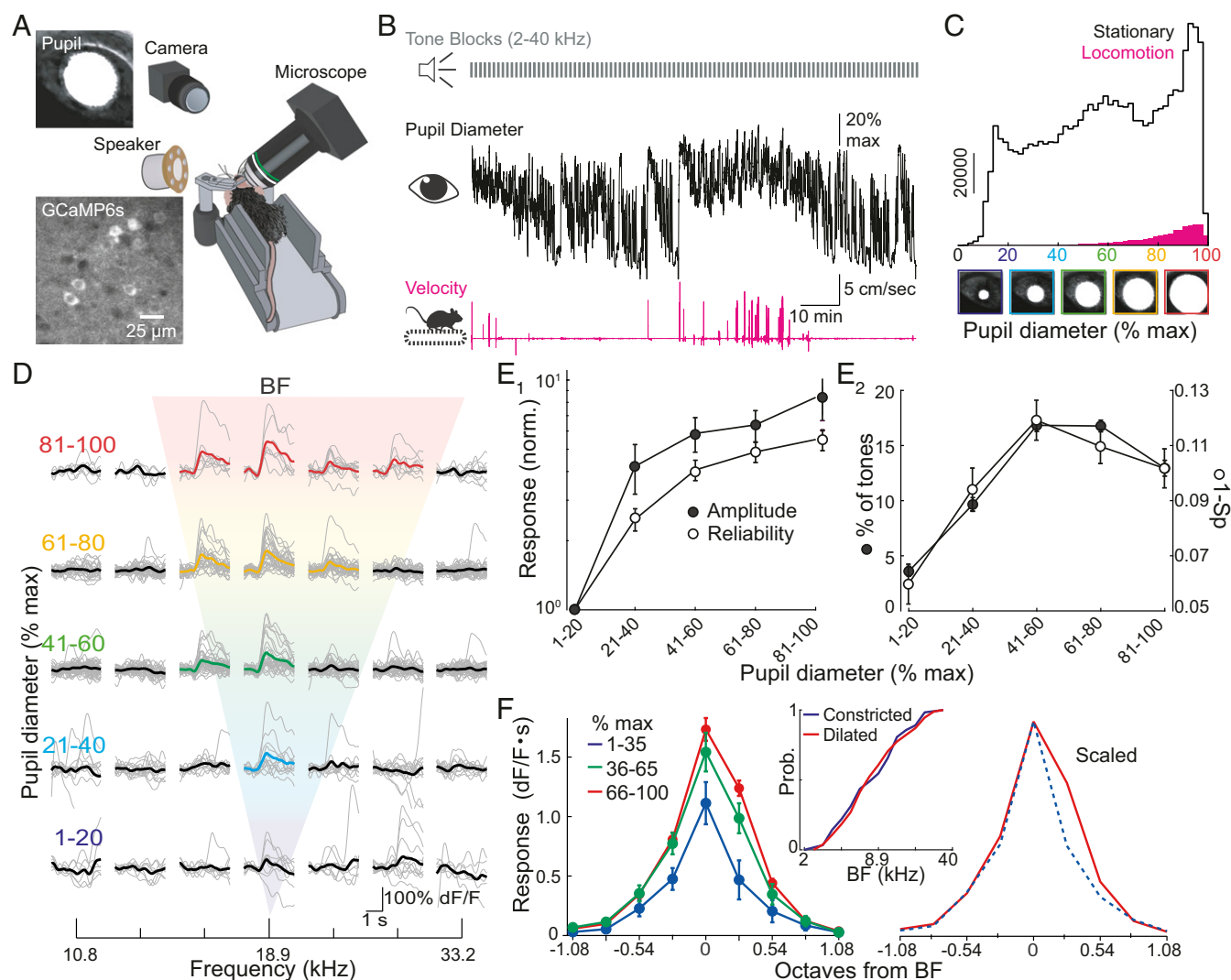


Fig. 1. Arousal modulates frequency tuning of L2/3 pyramidal cells. (A) Experiment schematic. An IR camera records pupil size (Top Left) during imaging of GCaMP6s-expressing neurons (Bottom Left). (B, Top) Tones presented during imaging. (B, Middle) Pupil diameter for 1 experiment. (B, Bottom) Simultaneous recording of mouse velocity. (C) Summary of pupil diameters ($n = 8$ experiments) when mice were stationary (black) or walking (pink) shows that locomotion only occurred during high arousal and mice were typically stationary. (D) A representative cell showing enhancement of tone-evoked responses as arousal (pupil diameter) increases. Bold trace, average response. Colored bold traces indicate frequencies eliciting a significant response. Gray, individual trial. (E₁) Arousal increases the amplitude (filled circles) and reliability (open circles) of BF responses ($n = 195$ cells). (E₂) Arousal increases percentages of tones evoking significant responses (filled circles) and reduces lifetime sparseness (Sp) (1-Sp, open circles). (F) Arousal broadens frequency tuning curves. (Left) Average tuning ($n = 195$ cells) during low (blue), moderate (green), and high (red) arousal aligned to low arousal BF. (Right) Low and high arousal curves scaled. (Middle) Cumulative probability plots show no shift in BF (1–35% [Constricted] vs. 66–100% [Dilated] maximum diameter, $n = 119,186$ cells). Error bars, SEM.

changes in response strength led to a marked increase (Friedman's ANOVA, $P < 0.001$) in the broadness of frequency tuning of individual cells: The number of tones eliciting significant responses peaked at moderate arousal levels (41–60% of maximal pupil diameter, Fig. 1E₂). Similar results were obtained using lifetime sparseness (18) (Friedman's ANOVA, $P < 0.001$), a tuning measure that does not require thresholding (Fig. 1E₂). We examined whether arousal modulates the shape of frequency tuning curves by centering cell responses to their BF at low arousal (Fig. 1F). Intriguingly, increases in arousal widened frequency tuning curves ($n = 119$ cells; 2-way ANOVA, P_{arousal} , $P_{\text{frequency}}$, and $P_{\text{arousal} \times \text{frequency}}$ interaction < 0.001) in an asymmetric fashion: responses to frequencies $> \text{BF}$ were more strongly enhanced than responses to frequencies $< \text{BF}$ (low vs. high arousal post hoc comparisons, $P = 0.06$ and < 0.001 for -0.27 octaves and $+0.27$ octaves from BF, respectively). Despite arousal-dependent changes in the symmetry of tuning curves, the BF of individual cells

remained constant (Kolmogorov–Smirnov test, $P = 0.94$, Fig. 1F). These results indicate that arousal strongly shapes the strength of tone-evoked responses and broadens frequency tuning in L2/3.

We next considered how arousal-dependent changes in pyramidal cell response properties contribute to sensory representations in A1. Consistent with the increases in response strength and tuning broadness, the fraction of cells responding to tones increased with arousal (Friedman's ANOVA, $P < 0.001$, Fig. 2A and B). These results indicate that arousal shapes the relative sparseness of sensory representations at the population level.

How do arousal-related changes in sensory representations impact the ability of the pyramidal cell population to discriminate frequencies? At face value, the reduction in sparseness of activated cells and broadening of frequency tuning should increase overlap in cell ensembles activated by different frequencies. This implies that increased arousal would degrade rather than improve frequency discrimination. To address this, we analyzed interneuronal

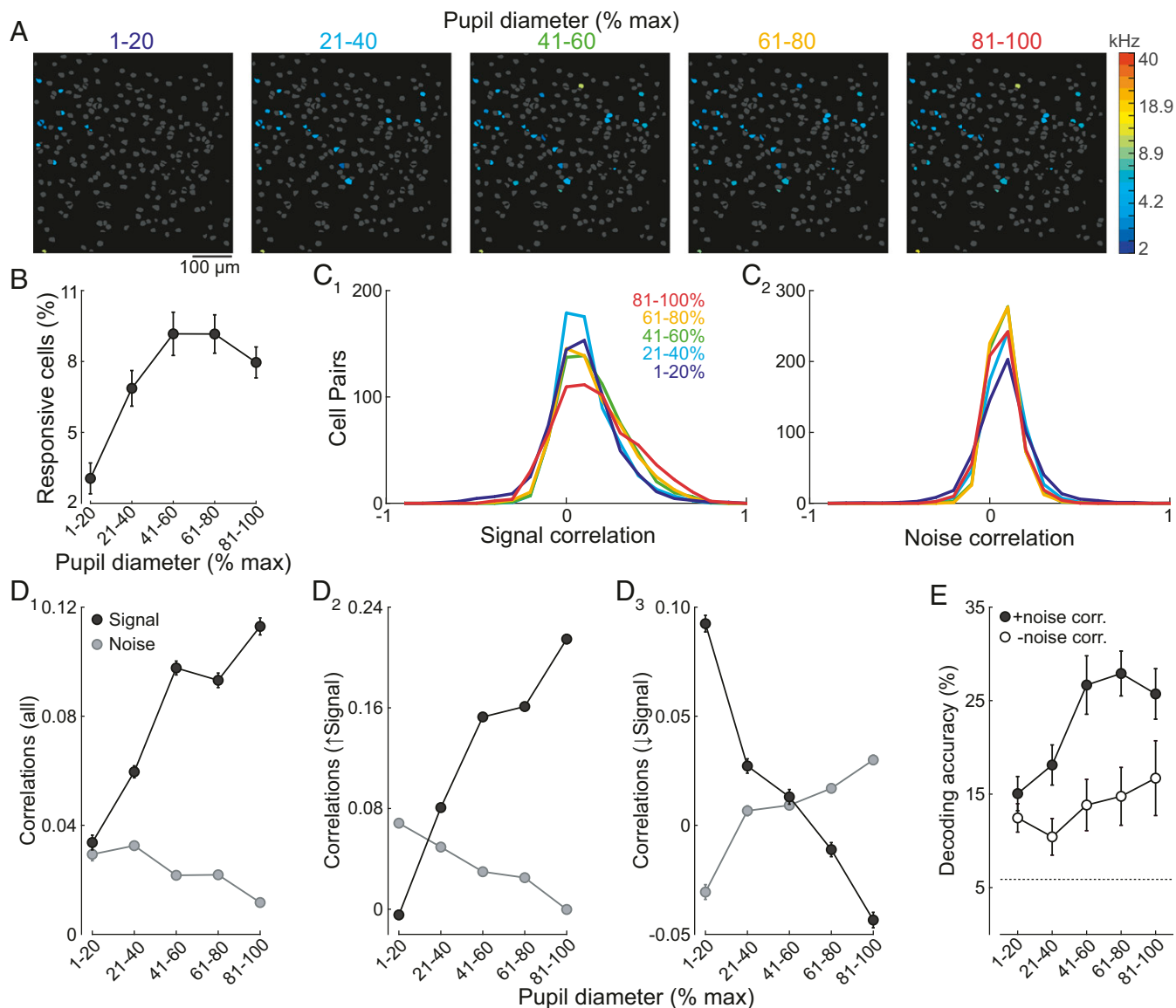


Fig. 2. Elevated arousal decreases sparseness of tone representations and improves frequency discrimination via modulation of noise correlations. (A) Increased arousal results in more tone-responsive cells. Responsive cells color coded by BF within the same field at different levels of arousal. Nonresponsive cells, gray. (B) Summary of tone responsiveness ($n = 8$ fields). (C₁) Increased arousal results in broader r_{signal} distributions and narrower r_{noise} distributions (C₂, $n = 4,938$ cell pairs). (D₁) Arousal differentially modulates r_{signal} (black) and r_{noise} (gray). (D₂) For the majority of cell pairs ($n = 3,086$), arousal increases r_{signal} and decreases r_{noise} . (D₃) The opposite relationship can also be observed ($n = 1,852$). (E) Nonlinear classifier analysis reveals that arousal-dependent increases in decoding accuracy are due to changes in r_{noise} . Filled circles, r_{noise} intact. Open circles, r_{noise} removed. Error bars, SEM.

correlations that contribute to population coding: signal correlations (r_{signal}), a measure of tuning similarity between pairs of neurons and noise correlations (r_{noise}), a measure of how much the trial-to-trial response variability of a pair of neurons is correlated (19, 20). Consistent with previous studies in the auditory cortex (21–24), mean r_{signal} and r_{noise} values were small and positive ($n = 4,938$ cell pairs, 8 experiments, Fig. 2C and D₁). Interneuronal correlations were significantly modulated by arousal (Fig. 2C, 2-way ANOVA, $P_{\text{arousal}}, P_{\text{correlations}}$, and $P_{\text{interaction}} < 0.001$). Across all cells, r_{signal} increased markedly as pupils became more dilated (Fig. 2D₁). This indicates that the tuning of pyramidal cells became more similar as arousal increased, consistent with the notion that elevations in arousal could degrade frequency discrimination. However, r_{noise} fell as arousal increased (Fig. 2D₁). Previous work has established that reducing r_{noise} should enhance sensory discrimination when cell pairs exhibit more similar tuning but impair discrimination when

tuning becomes dissimilar (19, 20, 24–26). Intriguingly, we found that arousal-dependent changes in r_{noise} were highly selective: r_{noise} decreased specifically in cell pairs that became more similarly tuned (increase in r_{signal}) as arousal increased (2-way ANOVA, $P_{\text{arousal}}, P_{\text{correlations}}$, and $P_{\text{interaction}} < 0.001$, Fig. 2D₂). In contrast, r_{noise} increased specifically for cell pairs in which elevated arousal led to a reduction in r_{signal} (2-way ANOVA, $P_{\text{arousal}}, P_{\text{correlations}}$, and $P_{\text{interaction}} < 0.001$, and $P_{\text{interaction}} = 0.066$, Fig. 2D₃). Together, these relationships between r_{signal} and r_{noise} predict that increases in arousal should enhance frequency discrimination by L2/3 cell populations.

To investigate the net effect of arousal on frequency discrimination, we used a nonlinear classifier (K-nearest neighbors', *Materials and Methods*). To specifically investigate the contribution of arousal-dependent changes in noise correlations to frequency encoding, the temporal order of responses was shuffled such that noise correlations were abolished while the frequency

identity for each tone trial remained unchanged. As expected, the decoder performed above chance level (5.9%) independent of arousal for both the unshuffled and the shuffled datasets. More importantly, decoding accuracy improved significantly (Fig. 2E) only when the data were unshuffled (2-way ANOVA with post hoc multiple comparisons, $P_{\text{arousal}}, P_{\text{dataset}} < 0.001$, and $P_{\text{interaction}} = 0.127$). Thus, changes in noise correlations play an important role in improving frequency discrimination as arousal increases.

We next used whole-cell recording to measure how arousal impacts subthreshold activity in L2/3 cells. Studies in many cortical areas indicate that spontaneous membrane potential (V_m) dynamics are influenced by brain state (reviewed in ref. 1). Indeed, during low to moderate arousal, current-clamp recordings revealed large-amplitude low-frequency (2–10 Hz) V_m fluctuations that were attenuated at high levels of arousal (Fig. 3A₁ and A₂). Both V_m SD and low-frequency oscillations (2–10 Hz power) diminished during high arousal ($n = 10$, Friedman's ANOVA, $P = 0.025$ and 0.020 , respectively, Fig. 3A₃), consistent with previous studies tracking locomotion or pupil diameter in V1 and A1 (7, 8, 10, 11, 14). Similar to deep layer neurons in A1 (14), mean V_m was slightly more hyperpolarized during moderate arousal ($n = 26$, Friedman's ANOVA, $P = 0.019$, Fig. 3A₄). Despite the similarity in mean V_m during the lowest and highest levels of arousal, the rate of spontaneous spiking steadily declined as arousal increased ($n = 18$, 7 whole-cell and 11 cell-attached recordings, Friedman's ANOVA, $P = 0.005$, Fig. 3A₄). Together, these findings are consistent with the idea that

low arousal is associated with high V_m variability and slow synchronized cortical activity while high arousal enforces low variability, suppression of slow rhythms and fewer spontaneous spikes (1, 5, 7, 15).

In agreement with recent work characterizing lateral inhibition in A1 (27), tones (100–200 ms) at “preferred” frequencies evoked short-latency excitatory postsynaptic potentials (EPSPs) while distal (“nonpreferred”) frequencies evoked a slow hyperpolarization (Fig. 3B). Interestingly, the time course of responses to preferred tones was arousal dependent. Averaging responses during low arousal revealed that the short-latency EPSP was curtailed by membrane hyperpolarization (Fig. 3B). During higher arousal, although the early amplitude of the EPSP slightly increased, the EPSP duration was markedly prolonged. For responses at nonpreferred frequencies, the tone-evoked hyperpolarization was strongly suppressed as arousal increased (Fig. 3B). Given the small change in the early EPSP, the most parsimonious explanation for the increased duration of preferred responses is the suppression of the overlapping slow hyperpolarization.

We quantified arousal-dependent changes in tone-evoked responses across cells by aligning responses to each cell's BF (Fig. 3C₁). On average, increases in arousal were associated with modest increases in EPSP peak amplitude ($n = 15$, 2-way ANOVA, $P_{\text{frequency}} < 0.001$, $P_{\text{arousal}} = 0.033$, and $P_{\text{interaction}} = 0.994$, Fig. 3C₂). However, arousal had a strong effect on the response integral and duration of tone-evoked EPSPs. During

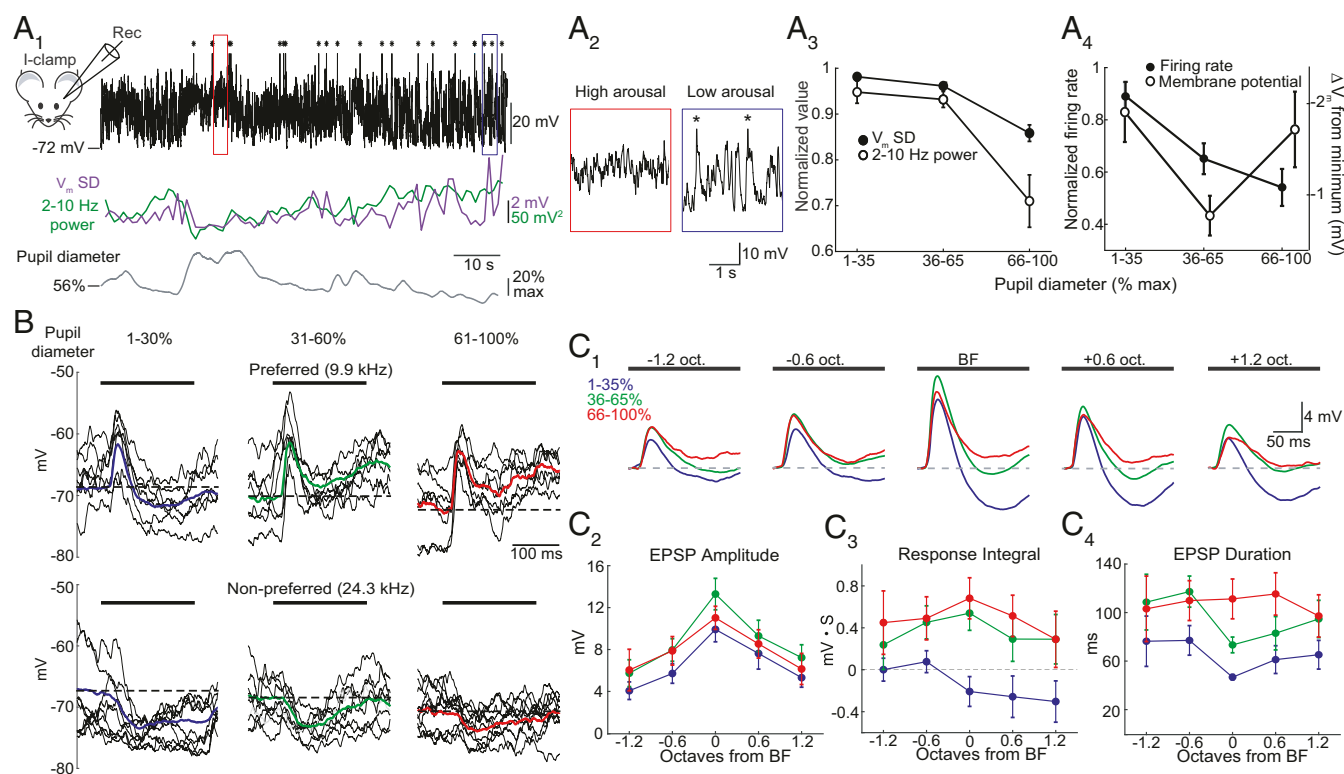


Fig. 3. Elevated arousal reduces membrane potential variability, spontaneous firing, and lateral inhibition. (A₁, Top) Current-clamp recording of membrane potential (V_m) in a representative L2/3 cell. Asterisks mark truncated action potentials. (Middle) V_m SD (purple) and 2–10 Hz power (green) over 1 s intervals. (Bottom) Pupil diameter. (A₂) Expansion of areas marked in A₁. (A₃) Summary showing that as arousal increases, 2–10 Hz power (open circles) and SD (filled circles) decrease. (A₄) Summary showing that spontaneous firing decreases as arousal increases (filled circles, $n = 19$). Mean V_m is most hyperpolarized during moderate arousal (open circles, $n = 30$ cells). (B) Responses to a preferred (Top) and nonpreferred (Bottom) tone (black bar) during different arousal levels in a representative cell. Gray, subset of single trials. Bold, mean response. Dashed line, baseline V_m . (C₁) Average responses to tones aligned to BF of each cell during low (blue), moderate (green), and high (red) arousals ($n = 15$ cells). Dashed line, baseline V_m . (C₂) Arousal causes a modest increase in EPSP peak amplitude. (C₃) Responses shift from net hyperpolarization to net depolarization for tones $\geq$ BF. (C₄) Arousal-dependent suppression of lateral inhibition increases EPSP duration. Error bars, SEM.

low arousal, tone-evoked hyperpolarization was most prominent during BF tones (frequencies with the strongest early EPSP) and those of higher frequencies. As arousal increased, suppression of the slow hyperpolarization shifted the integrated responses from net hyperpolarization to net depolarization (2-way ANOVA, $P_{\text{frequency}} = 0.458$, $P_{\text{arousal}} < 0.001$, and $P_{\text{interaction}} = 0.943$, Fig. 3C₃) and EPSP duration was prolonged (2-way ANOVA, $P_{\text{frequency}} = 0.303$, $P_{\text{arousal}} < 0.001$, and $P_{\text{interaction}} = 0.806$, Fig. 3C₄). Interestingly, the differences in response integral and EPSP duration between low and high arousal states were largest for frequencies $\geq$ BF (Fig. 3C₃ and C₄). Together, these results indicate that arousal can regulate response strength by reducing a form of lateral inhibition that limits the duration of tone-evoked synaptic excitation.

What accounts for the arousal-dependent changes in tone-evoked synaptic potentials? To address this question, we used voltage clamp to isolate excitatory postsynaptic currents (EPSCs) in L2/3 cells ($V_{\text{hold}} = -70$ mV, near the reversal potential for inhibition set by our internal solution). Under resting conditions, cells received high-frequency barrages of spontaneous EPSCs (Fig. 4A). On individual trials, preferred tones evoked transient EPSCs locked to tone onset (ON response). During low arousal, transient ON responses were immediately followed by a sustained suppression of spontaneous EPSCs. When trials were averaged, this resulted in a slow outward current (relative to baseline). We have recently shown (27) that this reflects a reduction in ongoing recurrent activity, “network suppression (NS),” underlying an unconventional form of lateral inhibition

that shapes frequency tuning. Indeed, during low arousal, NS was strongest at nonpreferred frequencies (Fig. 4A and E₁). Thus, the slow tone-evoked hyperpolarization in current-clamp recordings is due to a suppression of recurrent excitation rather than direct synaptic inhibition (27). Intriguingly, while early ON responses were only slightly modulated, NS was strongly attenuated when arousal increased (Fig. 4A and C–E). This loss of NS led to an increase in duration of ON responses (Fig. 4A). These results suggest that NS limits the strength of tone-evoked excitation in an arousal-dependent manner.

One explanation for the arousal-dependent attenuation of NS is that elevated arousal itself suppresses spontaneous excitation. In other words, during high arousal, there might be less synaptic input to suppress. We, thus, examined the relationship between arousal and spontaneous activity. Consistent with membrane voltage recordings, barrages of large-amplitude EPSCs during low arousal became desynchronized when arousal increased (Fig. 4B₁ and B₂). Although this led to a marked change in current variability (Friedman’s ANOVA, $P < 0.001$), total current (mean I_m) remained constant (Friedman’s ANOVA, $P = 0.223$, and $n = 14$ cells, Fig. 4B₃ and B₄). Thus, while excitatory input was more variable on a moment-to-moment basis during low arousal, the net amount of ongoing synaptic excitation remained the same as arousal increased. This indicates that arousal-dependent changes in NS cannot be due to changes in the available amount of recurrent excitation.

Given that inhibitory interneurons are highly interconnected with recurrent excitatory circuits, changes in NS should also

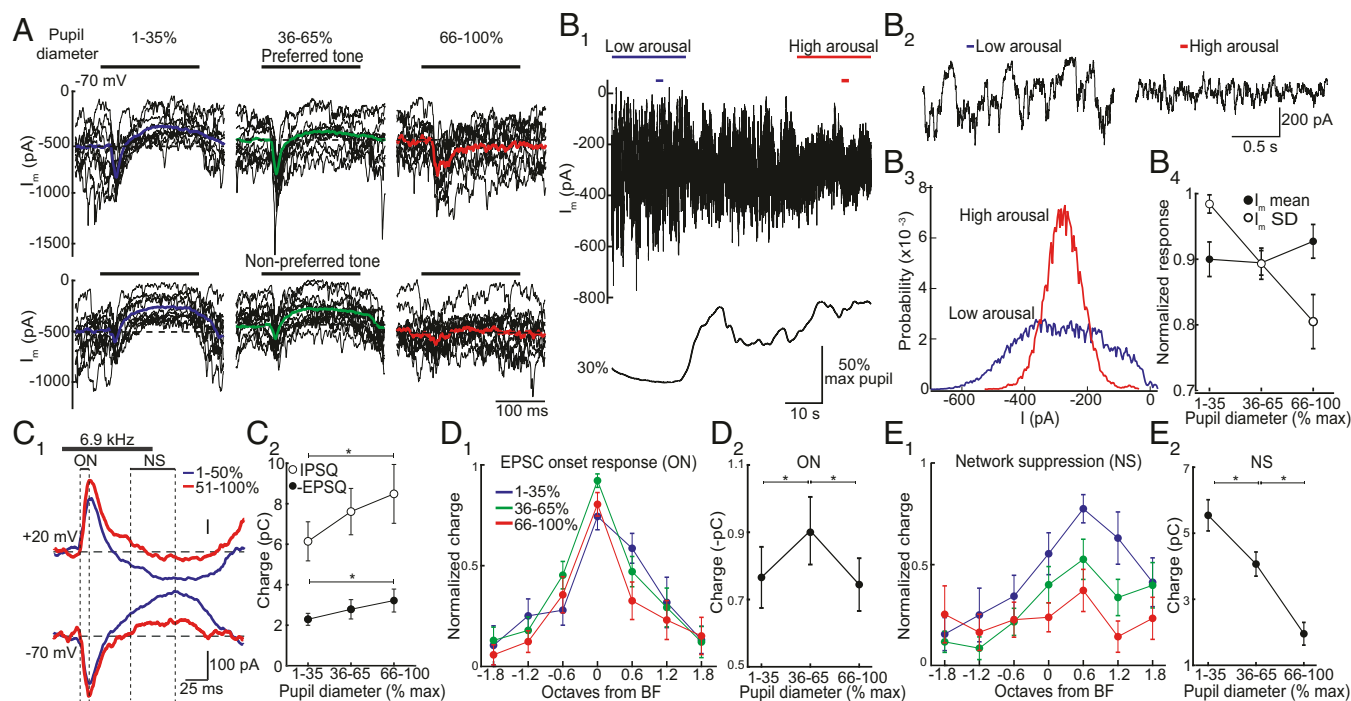


Fig. 4. Arousal modulates network suppression underlying lateral inhibition. (A) EPSCs in response to a preferred (*Top*) and nonpreferred (*Bottom*) tone during different arousal levels from 1 cell. Gray traces, subset of single trials. Bold traces, average. Dashed line, baseline. (B) Loss of network suppression is not due to less spontaneous excitation. (B₁) Current (–70 mV) and pupil diameter from 1 cell show a decrease in current variability during increased arousal. (B₂) Expansion of periods marked by small bars in B₁. (B₃) All points histogram of current (20 s) from B₁. (B₄) Increases in arousal decrease current variability (I_m SD) while mean current is unchanged ($n = 14$ cells). (C) Arousal modulates EPSCs and IPSCs similarly. (C₁) Averaged tone-evoked EPSCs and IPSCs from the same cell during different arousal states. (C₂) Absolute charge above (below) baseline for IPSCs (EPSCs) during different arousal levels ($n = 35$ tone responses at each arousal level, 12 cells, $*P = 0.010$ and 0.048 , respectively, paired t test). (D) EPSC onset (ON) responses in C₁ peak during moderate arousal. (D₁) Normalized ON responses aligned to BF ($n = 16$ cells). (D₂) Summary of all significant ON responses recorded at each arousal level shows that ON component increased from low to moderate arousal and then decreased during high arousal ($*P < 0.003$, paired t test, and $n = 32$ frequencies, 16 cells). (E) NS of EPSCs (in C₁) was biased to high frequencies and decreased monotonically with increasing arousal. (E₁) Normalized NS aligned to BF ($n = 16$ cells). (E₂) Summary of significant responses shows that NS steadily decreased with increases in arousal ($*P < 0.001$, paired t test, and $n = 27$ frequencies, 11 cells). Error bars, SEM.

impact tone-evoked synaptic inhibition (27). We, thus, compared the effect of arousal on tone-evoked EPSCs ($V_{\text{hold}} = -70$ mV) and inhibitory postsynaptic currents (IPSCs, $V_{\text{hold}} = +20$ mV, near the reversal potential for excitation) in the same cells ($n = 12$). Tone-evoked NS of IPSCs mirrored suppression of EPSCs (Fig. 4C₁). Moreover, arousal-dependent changes in the strength of tone-evoked excitation and inhibition (total charge below and above baseline, respectively) scaled such that the relative balance of excitation/inhibition remained constant (1.38- and 1.40-fold changes from low to high arousal states for IPSCs and EPSCs, respectively, Fig. 4C₂).

We next considered how arousal modulated the tuning of tone-evoked excitation. Overall, short-latency ON responses were largest during moderate arousal ($n = 16$ cells, Fig. 4D₁ and D₂). However, changes in arousal did not have an obvious impact on ON response tuning (2-way ANOVA, $P_{\text{frequency}} < 0.001$, $P_{\text{arousal}} = 0.236$, and $P_{\text{interaction}} = 0.585$). In contrast, increases in arousal led to a stronger monotonic attenuation of tone-evoked network suppression (2-way ANOVA, $P_{\text{frequency}} < 0.002$, and $P_{\text{interaction}} = 0.539$, Fig. 4E₁ and E₂). Furthermore, the arousal-dependent change in NS appeared tuned to frequencies $\geq$ BF. This reflects the fact that NS itself is biased to high frequencies (27). Together, these results indicate that, while arousal weakly modulates short-latency excitation, it has a strong impact on tone-evoked responses via regulation of an indirect form of inhibition that gates recurrent excitation.

Discussion

In this study, we used pupillometry, Ca^{2+} imaging, and intracellular recording in stationary mice to investigate arousal-related changes in frequency-tuned activity in A1. Imaging activity evoked by pure tones in L2/3 pyramidal cells revealed that arousal-dependent increases in response amplitude and reliability decreased the sparseness of cortical tone representations. Consistent with these changes, signal correlations increased with arousal indicating greater overlap in the frequency-tuning curves of cells across the cortical population. Despite this increase in tuning similarity, elevated arousal improved frequency discrimination by cell ensembles due to a reduction in noise correlations (shared trial-to-trial variability). Similar to previous studies (1, 7, 11, 14), increases in arousal caused a shift in spontaneous synaptic activity: slow (2–10 Hz) bursts of excitatory input gave way to steady desynchronized input. Slow oscillations in spontaneous activity can be correlated between nearby cells as well as across wide areas of the sensory cortex (28). Therefore, we think it likely that the arousal-dependent shift in membrane dynamics is largely responsible for the reduction in noise correlations underlying improved frequency discrimination.

Increases in arousal were associated with a reduction in frequency of spontaneous action potentials, raising the possibility that the changes in sensory representations we observed simply reflect an enhanced signal-to-noise-ratio (SNR). Indeed, the arousal-dependent increase in response strength and reliability as well as the reduction in sparseness could be due to an improved SNR. However, increases in arousal also broadened frequency-tuning curves of individual cells due to a stronger enhancement of frequencies $>$ BF. Thus, while changes in SNR are likely to contribute to modulation of cortical tone representations, SNR alone cannot explain the effects of arousal on frequency tuning.

We used current- and voltage-clamp recordings to examine how arousal-dependent changes in tone-evoked subthreshold activity could modulate tuning properties. Interestingly, conventional short-latency tone-evoked synaptic excitation was affected by arousal in a nonmonotonic fashion. Transitions from low to moderate arousals led to a modest increase in the strength of short-latency evoked EPSCs, however, response strength subsequently declined during high arousal. Activity evoked by complex sounds in deep layers of A1 is similarly found to be

maximal during moderate arousal (14). Nonetheless, the small arousal-related increases in conventional short-latency synaptic input seem insufficient to account for the strong changes in activity observed with Ca^{2+} imaging.

We show here and in recent work in awake mice (27) that nonpreferred tones can evoke a pure inhibitory response due to a slow suppression of ongoing recurrent synaptic excitation. This network suppression relies on cortical somatostatin-expressing interneurons and provides an unconventional form of lateral inhibition (27). Recent work in V1 indicates that surround suppression also reflects a reduction in total network input due to somatostatin interneurons (29). Here, we show that NS is strongest during low arousal and becomes progressively weaker as arousal increases. Furthermore, the arousal-dependent loss of NS at preferred frequencies leads to an increase in duration of tone-evoked responses. Intriguingly, NS occurs preferentially for tones $>$ BF (27). Although the reasons for this asymmetry are yet to be established, the net effect of the strong reduction in NS by arousal is a preferential change in synaptic responses to high-frequency tones. This asymmetry in NS is likely to account for why increases in arousal broaden frequency tuned L2/3 cell output with a high-frequency bias.

Materials and Methods

Mice [8–16 wk old, Emx1-Cre (Jackson Laboratories No. 05638), Ai94(TITL-GCaMP6s)-D;CaMK2a-tTA (Jackson Laboratories No. 024115) or wild-type C57Bl/6] were housed with a 12:12 h reversed light cycle. Experiments were performed during the dark period. All procedures were in accordance with protocols approved by the University of California San Diego Institutional Animal Care and Use Committee and guidelines of the National Institutes of Health.

Surgical Preparation. For imaging, mice were anesthetized with isoflurane and received dexamethasone (2 mg/kg, i.m.). A custom head bar was glued to the skull, muscle overlying the right auditory cortex was removed, and a craniotomy ($\sim 2 \times 3$ mm) was performed over the auditory cortex, leaving the dura intact. A glass window was placed over the craniotomy and secured with dental acrylic. Mice received baytril (10 mg/kg) and buprenorphine (0.1 mg/kg) before returning to their home cages. Mice were habituated to sitting quietly while head fixed for 2–7 d (2 h/day) before imaging.

For electrophysiology, 1–3 d after head-bar implantation and habituation to head fixation, mice were anesthetized with isoflurane, and the skull above A1 identified by intrinsic imaging (30) was thinned using a drill. During thinning, the skull was flushed with cold artificial cerebrospinal fluid ([aCSF], [in millimoles] 142 NaCl, 5 KCl, 10 glucose, 10 Hepes, 3.1 CaCl_2 , 1.3 MgCl_2 , pH 7.4, 310 mOsm). After thinning, mice received dexamethasone (2 mg/kg) and recovered in their home cage for > 2 h. Immediately prior to recording, a well filled with aCSF was constructed around the recording site, a small (< 0.3 mm) craniotomy was performed in the thinned skull, and the dura removed.

Pupillometry and Locomotion Tracking. The eye contralateral to imaging or recording was monitored via a camera (BFLY-U3-0552M-CS, Point Gray). For electrophysiology experiments, an IR LED was used to visualize the pupil in the presence of weak ambient illumination (473 nm). Locomotion was monitored by a passive treadmill fitted with a rotary encoder (Janelia). Pupil measurements and velocity were acquired using open-source software (Bonsai, <http://bonsai-rx.org/>). Pupil diameter values were smoothed using a moving average filter (1 s). Locomotion epochs (nonzero velocity for > 0.5 s) were excluded from analysis. Pure tones were delivered via a calibrated free-field speaker (ES1, TDT) directed to the ear contralateral to imaging or recording. Tones were generated by software (BControl; <http://brodylab.org>) running on MATLAB (MathWorks) communicating with a real-time system (RTLinux).

In Vivo Two-Photon Ca^{2+} Imaging. Imaging was performed within 2 to 3 wk of window implantation. Imaging fields were within A1 determined from intrinsic signal imaging. GCaMP6s was excited at 950 nm (Mai Tai, Newport), and images (512×512 pixels covering $\sim 500 \times 500 \mu\text{m}$) were acquired at 28.4 Hz with a 16x objective (Nikon) using a commercial microscope (B-scope, Thorlabs) and ScanImage4. Images were acquired 120–250 μm below the dura, and lateral motion was corrected using a phase correlation algorithm (<https://github.com/cortex-lab/Suite2P>).

Imaging Analysis. Responses were classified as significant if $P < 0.005$ (Wilcoxon rank sum test) for $>85\%$ of trial-pooled timepoints over any continuous 0.5 s window during the 1 s tone, compared to a trial-pooled 1 s period preceding the tone. Cells were responsive if responses to, at least, 2 tones in, at least, 2 of 5 arousal levels (bin size 20% from 0 to 100% pupil max) were significant. Response strength was measured as the dF/F integral of the mean response of each cell during each arousal state, normalized to low arousal (1–20% pupil max). Reliability was measured as the mean pairwise trial-by-trial Pearson's correlation coefficient of responses during each arousal

state. Lifetime sparseness was $\left(1 - \left\{ \left[\sum_{j=1,N} r_j / N \right]^2 / \left[\sum_{j=1,N} r_j^2 / N \right] \right\} \right) / (1 - 1/N)$, where r_j was the response peak amplitude of the cell to tone j , and N was the total number of tones.

Total correlations (sum of signal and noise correlations) were quantified using a trial-by-trial response vector (dF/F integral during the tone) for each arousal level for each cell (31). To calculate r_{signal} , the temporal order of each cell's responses to repeated presentations of each tone were shuffled, abolishing noise correlations while maintaining trial-by-trial stimulus identity. Total and signal correlations were obtained by calculating Pearson's correlation coefficients for the unshuffled and shuffled response vectors, respectively, of cell pairs from the same experiment. A noise correlation value for each cell pair from each experiment was obtained by subtracting their signal correlation value from their total correlation value. To determine if arousal modulates r_{noise} in a r_{signal} -related manner, mean noise correlations were calculated separately for cell pairs with signal correlations that increased (slope > 0) or decreased (slope < 0) with arousal.

For the nonlinear classifier, a population response matrix was created from the trial-by-trial responses for all cells of each experiment. The response matrices for a subset of randomly selected trials (75% of total) were used to train a K-nearest neighbors' classifier ($k = 10$ trials; standardized Euclidean distance metric) before testing the performance of the classifier on the remaining 25% of trials (100 iterations).

Whole-cell recording. Recordings were made using the blind technique (32). Current-clamp recordings used pipettes filled with internal solution containing

(in millimoles) 130 Kgluconate, 5 NaCl, 10 Hepes, 12 Na-phosphocreatine, 0.2 EGTA, 3 Mg-ATP, and 0.2 Na-GTP (pH 7.2, 305 mOsm). Voltage-clamp recordings used pipettes filled with (in millimoles) 130 Csgluconate, 10 Hepes, 5 TEA-Cl, 12 Na-phosphocreatine, 0.2 EGTA, 3 Mg-ATP, and 0.2 Na-GTP (pH 7.2, 310 mOsm). Series resistance ($R_s < 50$ MOhms) was continuously monitored for stability. Recording depth ($226 \pm 11.3 \mu\text{m}$ from pia, $n = 31$) was determined from the micromanipulator z axis readout (MP-285, Sutter Instrument). Recordings were made with a Multiclamp 700A (Molecular Devices), digitized at 5–20 kHz, and acquired using AxoGraph. Potentials were not corrected for the liquid junction potential (~ 15 mV).

Responses were sorted by pupil diameter during the tone (1–35%, 36–65%, and 66–100%), averaged (≥ 5 trials) for each frequency, and baselined to tone onset. Cells were rejected if no ON response was >30 pA or >2 mV (voltage and current clamps, respectively). For current-clamp recordings, integral and peak amplitudes were measured 10–200 ms posttone onset. EPSP duration was measured at 25% of the peak. BF was the frequency with fastest EPSP onset (slope). In voltage-clamp recordings, ON response was measured as charge in a window of 20–30 ms posttone onset. NS was calculated as charge below baseline 75–125 ms posttone onset. Excitatory I_m was measured relative to the most positive current value during each recording. Excitatory (inhibitory) charge above the baseline was calculated as the charge 10–100 ms posttone onset which was below (above) the baseline holding current. EPSC BF was determined from the peak amplitude of the response within 50 ms of tone onset. Cell responsiveness was determined with a Wilcoxon signed-rank test ($\alpha = 0.01$).

Data Availability. All data discussed in the paper will be made available to readers upon request.

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Arousal levels explain inter-subject variability of neuromodulation effects

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Abstract

Over the past two decades, the postulated modulatory effects of transcranial direct current stimulation (tDCS) on the human brain have been extensively investigated, with attractive real-world applications. However, recent concerns on reliability of tDCS effects have been raised, principally due to reduced replicability and to the great interindividual variability in response to tDCS. These inconsistencies are likely due to the interplay between the level of induced cortical excitability and unaccounted individual state-dependent factors. On these grounds, we aimed to verify whether the behavioural effects induced by a common prefrontal tDCS montage were dependent on the participants' arousal levels. Pupillary dynamics were recorded during an auditory oddball task while applying either a sham or real tDCS. The tDCS effects on reaction times and pupil dilation were evaluated as a function of subjective and physiological arousal predictors. Both predictors significantly explained performance during real tDCS, namely reaction times improved only with moderate arousal levels; likewise, pupil dilation was affected according to the ongoing levels of arousal. These findings highlight the critical role of arousal in shaping the neuromodulatory outcome, and thus encourage a more careful interpretation of null or negative results.

Keywords

tDCS; arousal; pupil; interindividual variability; neuromodulation; state dependency; transcranial electrical stimulation; tES.

1. Introduction

Founded on decades of experimentation, transcranial direct current stimulation (tDCS) is a research tool capable of interacting with the central nervous system, that has been rediscovered at the beginning of this century (1). Beside its value for basic research (2), tDCS has raised great interest for real-world applications, like rehabilitative interventions for neurological and psychiatric diseases (3) and cognitive enhancement (or detracting) in both young and older adults (4–7). However, the development of more effective and generalizable stimulation protocols has been hindered by the gap between our sparse knowledge of the physiological effects and the induced behavioral impact of tDCS (8). What raises most concern is the lack of replicability among tDCS studies and the interindividual variability in response to tDCS (9–15). In addition to non-optimal methodological practices, such as inadequate control conditions and lack of statistical rigor, a complex interplay among biological differences and the level of neuromodulatory effects might be crucial in explaining the reported inconsistencies across studies (16–18). In particular, state-based factors, including the specific or generalized levels of activation prior and during stimulation, the initial levels of performance, wakefulness, task priming or novelty, might all play a decisive role. It appears conceivable to interpret the final effects of tDCS as contingent on the level of network engagement (19,20). In line with this prediction, several cognitive studies have reported a clear effect of baseline levels of different mental capabilities on tDCS response (21–26). Most recently, individual differences in the behavioral effects of prefrontal tDCS have been associated with the levels of excitability of the targeted cortex, indexed by relative concentrations of GABA and glutamate (27).

Notably, tDCS affects large-scale brain systems extending well beyond the area under the stimulating electrode (28–31). This approach translates into a lack of focality that closely resembles the spread of the noradrenergic modulatory action exerted by the locus coeruleus (LC), which subtends arousal functions. Several authors have highlighted the key adaptive role of this specific midbrain system in shaping behavioral performance of primates (32–36). A large body of evidence suggests that the

exogenous direct currents and the endogenous noradrenergic modulatory action on target cells, share the same central mechanism of neuronal gain control (34,37–39). Therefore, an interrelation between the two stimulating activities seems reasonable to the extent that whenever the contrast between activated and inhibited units becomes sufficiently increased or decreased any further added neuromodulation can likely spoil the expected results. In this regard, a recent study has shown that offline anodal tDCS may hinder the LC endogenous action during response inhibition processes due to the induced alterations of pre-existent neural excitability levels (40). Given the above considerations, it appears evident that great part of the tDCS behavioral variability reasonably stems from the interdependency between the induced cortical excitability and the varying levels of arousal experienced by participants before and during the experimental sessions.

The aim of this study was to verify whether the behavioural and physiological responses induced by a common prefrontal tDCS montage were dependent on the participants' arousal levels. We selected the tDCS montage used to stimulate prefrontal cortex in attentional and vigilance tasks (40–43), which is also commonly used in a variety of other settings, such as language-related, executive functions, episodic and visual working memory tasks (44–47). The tDCS was applied during an auditory oddball task aimed to probe cognitive performance as a function of arousal levels (48–50). Our task, indeed, was purposefully designed to keep participants alerted over uncertain intervals (i.e., variable inter stimulus interval) in a way that online tDCS effects would be necessarily subjected to more frequent fluctuations of arousal (51,52).

We tracked pupillary changes as a proxy for the LC modulatory action (50,53–55). Accordingly, we used reaction times (RT) and pupil dilation peaks (PD) as measures of LC phasic response to the relevant stimuli (target), and pre-stimulus pupil diameter (PrePD) as a physiological marker of the LC tonic discharge activity. Furthermore, because LC endogenous activity is closely related to the perceived anxiety (56–58) subjective arousal levels were evaluated by means of State-Trait Anxiety Inventory (STAI-Y) (59).

2. Methods

Mindful that the mere sensory stimulation could mimic the expected arousal effects, prior to conducting the study, we ran a control experiment to validate our blind-controlled tDCS protocol with respect to the potential alteration of arousal due to subjective sensations. To this end, ten healthy participants were recruited. Pupillary dynamics were recorded at rest using the exact same setting as in our main experiment (see section 2.3 and 2.4). Statistical analyses revealed no difference in eye-blink rate and subjective discomfort between sham and real stimulation, ruling out the possibility of tDCS confounding effects on arousal (see supplementary material).

2.1 Participants

Fifteen right-handed healthy participants took part in the main experiment. Data of one subject were rejected prior to analyses due to the excessive noise in her/his pupil signal (i.e., interpolation rate > 30% of the whole epoch; see 2.3). The remaining 14 participants (8 females) had a mean age of 22.4 ($SD = 3.9$) and a mean score to the STAI-Y trait of 44.9 ($SD = 4.1$). Participants had no history of neurological or psychiatric illness and had normal or corrected-to-normal visual acuity. Ethical approval was obtained by the Ethics Committee of the IRCCS Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy. All participants were given written informed consent.

2.2 Study design and task procedure

A single-blind within-subject design was implemented for this experiment. The testing sessions were organized in two days separated by at least 48h in order to exclude any tDCS carryover effects. In each session we collected behavioral and pupil data for the whole task duration (~18 min). Participants completed the task twice: at *baseline* (T1) without any electrodes mounted on their scalp, and subsequently either during *sham* or *real* stimulation (T2) (Figure 1b). Participants were randomly assigned and counterbalanced across two session-orders of tDCS protocol, so as to rule out any extra confounding variable. Importantly, they were kept blind to the

ongoing experimental condition (i.e., sham or real). However, any proportion of variability possibly due to either orders of stimulation was accounted for by including the order group as an independent fixed factor (see section 2.5). As for the time of the day, the same participant was tested at around the same hour to control for any arousal variation due to the daily metabolic cycle and circadian rhythms (60).

Participants seated in a soundproof dark room at the distance of about 55 cm from a 17-in LCD monitor and with the only source of light provided by a grey fixation cross. The auditory oddball task was presented using E-Prime presentation software (61) by means of two constant-loudness speakers (Figure 1a).

In every task condition there was a fixed total number of trials (420) of which 20% included targets (84) and 80% standards stimuli (336). The stimuli order was then pseudorandomized in a way that target tones (880Hz) occurred after at least three standard tones (800 Hz). The interstimulus interval was set to a range of 2.1-2.9 s and both stimuli lasted for 70 ms including 5 ms of fade in-out edit. In so doing, we ensured enough time (~8 s) for any pupil dilation to return to baseline before overlapping to the next target trial (50,53). Along with a short training session, participants were instructed to readily press a button with their right index finger whenever detecting a target tone, and to keep their gaze on the fixation cross throughout the task. Speed of response and gaze fixation were emphasized before each task execution.

At the end of each experimental session participants were given a questionnaire to rate the perceived sensations or discomforts that influenced their performance (62,63).

Finally, a careful screening on the amount of sleep, caffeine intake, nicotine and alcohol consumption was carried out next to the above questionnaire. None of these factors was found to be associated with either stimulation sessions.

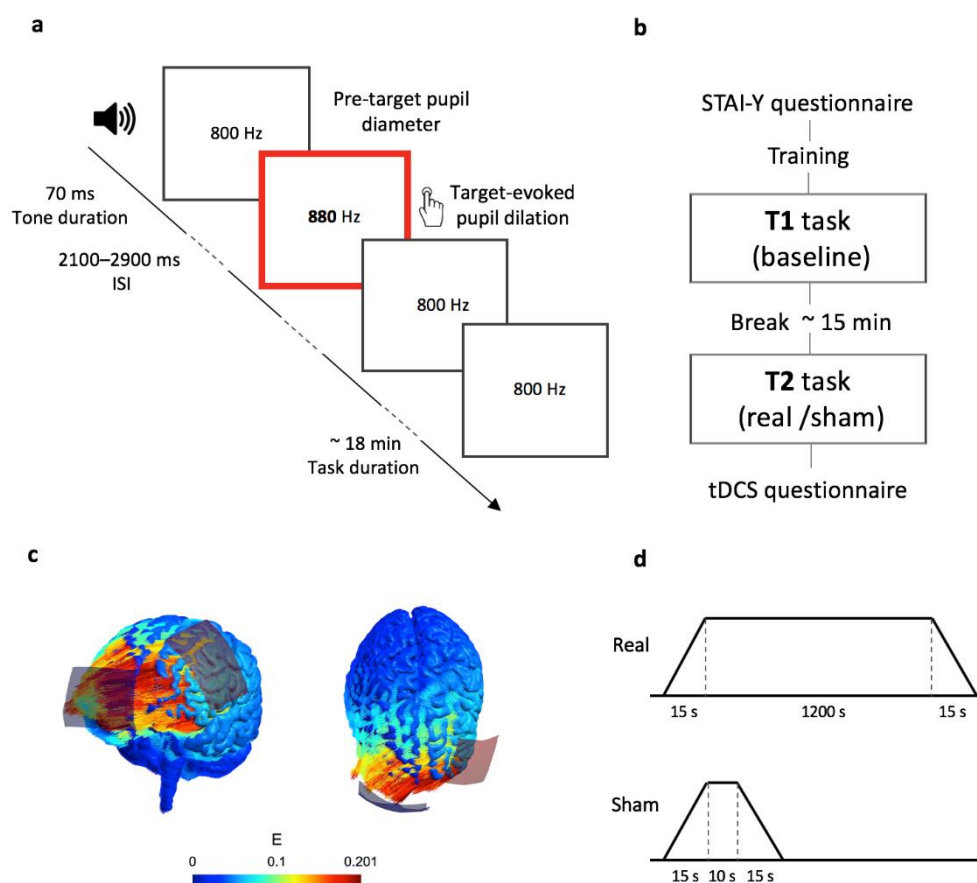


Fig. 1. Study design and task paradigm. **a**, Example of a trial sequence. **b**, Overview of the experimental timeline, showing two testing sessions each one with two task conditions: baseline and stimulation. **c**, Simulation results for the applied tDCS montage and parameters using SimNIBS toolbox (Saturnino et al., 2019). The colors denote the electric fields simulated in a default head model. **d**, Schematic representation of the stimulation protocol

2.3 Pupil signal recording and pre-processing

Participants seated on a chair with adjustable height allowing for the use of a fixed chinrest, and thus keeping variability in the eye-to-camera distance and visual angle as low as possible. For the pupil diameter recording, an EyeLink 1000 Plus system (SR Research, Osgood, ON, Canada) was set up at 500 Hz sampling rate with left-monocular and pupil-CR tracking mode. A 9-point calibration procedure was performed before each recording session. After the final session, participants were

asked to wear hand-crafted goggles whose left side incorporated an artificial eye with a 4 mm pupil, carefully positioned over the subject's left eye. This allowed for a precise conversion of pupil arbitrary units from the eye-tracker system output to millimeters. Pupil signal was processed offline. Eye blink correction was implemented with a custom script in MATLAB (MathWorks, Inc, Natick, MA, USA). A shape-preserving piecewise cubic interpolation method was chosen to interpolate values ranging from 70 ms before blink onset to 300 after blink offset. Epoch segmentation (-1 s to +2.5 s, relative to target onset), baseline correction (subtractive method, from -800 ms to +200 ms) and visual inspection of pupil traces was carried out in the Brain Vision EEG analyzer software (Brain Products GmbH, Munich, Germany). We extracted two variables of interest from pupil signal: (i) pupil dilation (PD), as the peak value of the maximum dilation after targets presentation and (ii) Pre-stimulus pupil diameter (PrePD) as the mean of 1 s data prior to tone presentation. All epochs with a peak pupil diameter exceeding ± 2 mm were rejected (50).

2.4 tDCS protocol

A battery-driven current stimulator (Brain- STIM, EMS, Bologna, Italy) was used to deliver 1 mA (0.028 mA/cm^2) direct current stimulation via two rubber electrodes (35 cm^2) which were inserted inside two saline-soaked sponges. These were fixated with an elastic mesh stretching over the entire head. In order to ensure a stable impedance level as well as keeping skin sensations at the minimum, conductive electro-gel was also applied. Similarly to previous studies (43), the electrodes montage consisted in placing the anode over the area F3 of the EEG 10-20 system and the return (cathode) electrode over the right supra-orbital area as reported in Figure 1c. The duration of the stimulation consisted of about 17 min (1040 s) with 15 s of currents fade-in and fade-out. Configuration of the sham condition included 15 s of fade-in, 10 s of actual current delivery and 15 s of fade-out given at the beginning of the experiment only (see Figure 1d).

2.5 Statistical analyses

As expected, the nature of our oddball task caused ceiling effects in the correct responses for all conditions (accuracy rate > 98%). All the trials that included either a false alarm or a missed response were left out from subsequent analyses on RT, as well as trials corresponding to RT faster than 150 ms or exceeding 1.96 standard deviations from the mean (number rejected trials: $M = 3.14$, $SD = 1.39$). All valid RT were then log-transformed to the base e in order to ensure a normal distribution of the data. We considered only trials having no missing values at the two main outcomes RT and PD, resulting in 52 trials overall. Importantly, these data points were not collapsed across conditions; hence *Trial* was included in the analyses as an independent fixed factor, and thus affording a greater reliability and robustness of the findings.

In order to study the effect of tDCS on the behavioral and physiological responses, we performed two linear mixed models (LMM) on RT and on PD as dependent variables. Individual (subject-specific) variation was accounted for by considering *Subjects* as random effect. Fixed effects, repeated within subjects, were specified for *Condition* (2 levels, *real* and *sham*), *Time* (2 levels, *T1* and *T2*) and *Trial* (52 levels); whereas *Order* (2 subgroups, *sham-real* and *real-sham*) was considered as a between-subject fixed effect. In addition, the interaction *Condition* x *Time* was assessed. Post hoc comparisons were adjusted with Sidak correction for multiple comparisons.

The above LMM were subsequently adjusted for subjective arousal (measured by STAI-Y State score) and for physiological arousal (evaluated by PrePD) in order to assess their effects on tDCS-induced modulation. Akaike information criteria (AIC) was used to select the best fitted models (the lower AIC the better model) and the corresponding predictors.

Finally, to control for any interdependence between the subjective and physiological measures of arousal, we calculated Pearson's (r) two tailed correlations between PrePD and STAI-Y State score. Correlations coefficients were all non-significant (p 's > 0.05). All statistical analyses were conducted on SPSS Statistics (IBM Corp, Armonk, NY, USA).

3. Results

Despite the random assignment, the participants included in the two *Order* subgroups exhibited different levels of physiological tonic arousal (PrePD) already at the baseline of the first experimental session, that is before applying the tDCS electrodes (two tailed independent t-tests [$t = -3.64$, $df = 11.82$, $p = .003$]). No difference was found between the subgroups in the STAI-Y scores [$t = -.41$, $df = 11.57$, $p = .68$].

As for the reported sensations, a Wilcoxon matched pair test revealed no significant difference between sham and real stimulation [$Z = 1.34$, $p = 0.18$]. It was also ensured that their written responses were consistent with their oral report. Therefore, it was safe to assume that participants were completely unaware of the type of stimulation protocol.

3.1 Reaction times – RT

The unadjusted linear mixed model on RT [AIC = -2574] revealed no significant effects of the *Order* [$F_{(1,11)} = .59$, $p = .477$] and a trend toward significance for *Condition* [$F_{(1,2419)} = 3.76$, $p = .053$] and *Trial* [$F_{(51,98)} = 1.47$, $p = .05$], with slower RT occurring at the end of each tasks. A significant effect of *Time* [$F_{(1,2399)} = 12.15$, $p < .001$] showed that performance significantly improved from *T1* [$M = 5.98$; $SE = .05$] to *T2* sessions [$M = 5.96$; $SE = .05$], indicating an overall practice effect. Importantly, we found a significant *Condition* x *Time* interaction effect [$F_{(1,2403)} = 12.08$, $p = .001$], indicating a different trend for real and sham conditions. The post-hoc comparison for *Time* revealed a significant performance improvement during *sham* ($p < .001$), but not during *real* stimulation ($p = .99$). This finding suggests that real tDCS hindered the practice effect that was present in the sham condition.

Next, LMM adjusted for STAI-Y and PrePD were separately performed (see Supplementary Table 1). We found an overall significant contribution of STAI-Y [$F_{(1,2312)} = 9.44$, $p = .002$] and more importantly a significant 3-way interaction [*Condition* x *Time* x STAI-Y: $F = 19.1$, $df = 3/1857$, $p < .001$], indicating that the subjective level of arousal affected the interaction *Condition* x *Time* on RT. Specifically, STAI-Y state scores were predictive of the performance variations across tDCS

conditions. During sham session a performance improvement was observed for all the continuum of arousal, although it diminished as the level of STAY-Y increased. In the real tDCS condition, RT proved to be faster only when the levels of arousal were low, whereas such pattern was abolished or even reversed with higher levels of arousal (i.e., higher STAI-Y scores, see Figure 2).

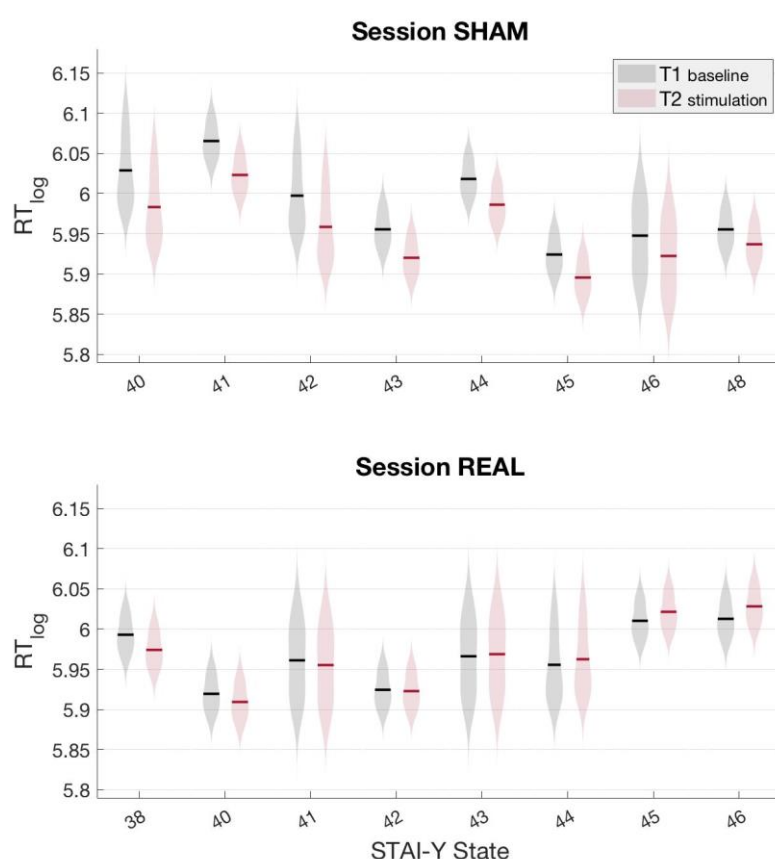


Fig. 2. Reaction times by subjective arousal. Average log-based RT of model fitted values are plotted as a function of STAI-Y scores, with results from session sham (top panel) and real (bottom panel). Each mean value is marked over the corresponding distribution of the data. Colors grey and red represent the baseline (T1) and stimulation (T2) task, respectively.

After adjusting for PrePD, *Condition* and *Time* remained significant [$F_{(1,2131)} = 6.88, p = .009$; $F_{(1,1967)} = 9.44, p = .032$ respectively], although the physiological predictor did not reach statistical significance [PrePD: $F_{(1,1834)} = 3.52, p = .061$]. Also in this case, the 3-way interaction [*Condition* x *Time* x PrePD: $F_{(3,1307)} = 5.57, p = .001$] revealed that the interaction between *Condition* and *Time*

was affected by participants' physiological level of arousal. Consistently with the aforementioned effects of subjective levels of arousal, RT improvement across time was consistent in the sham condition, but larger during trials with a reduced PrePD. During real tDCS, a trend toward lower or no improvement was observed as physiological arousal increased (see Figure 3).

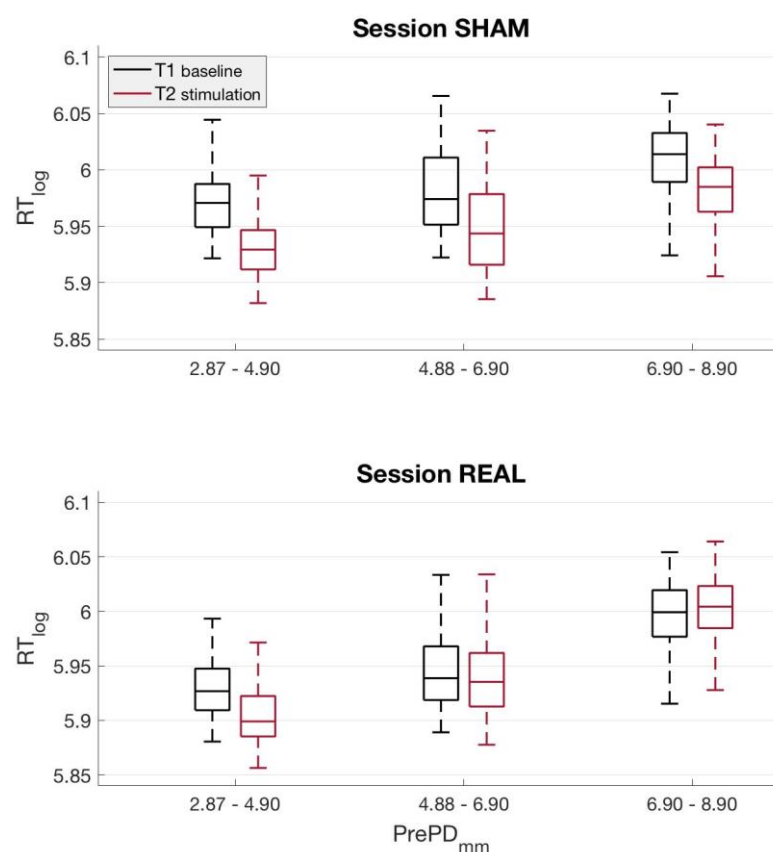


Fig. 3. Reaction times by physiological arousal. On each box, the interquartile range, the whiskers and the median of predicted log-based RT are represented for three linearly interspaced bins of pre-target pupil diameter, with results from session sham (top panel) and real (bottom panel). Colors grey and red represent the baseline (T1) and stimulation (T2) task, respectively.

Based on the present results, a far more consistent trend emerged from the adjusted models as compared to the same raw data (see Figure 4). This finding corroborates the importance of not disregarding discrepancies rooted in interindividual differences, such as in physiological and subjective arousal, but rather include them as predictors along with individual random effects.

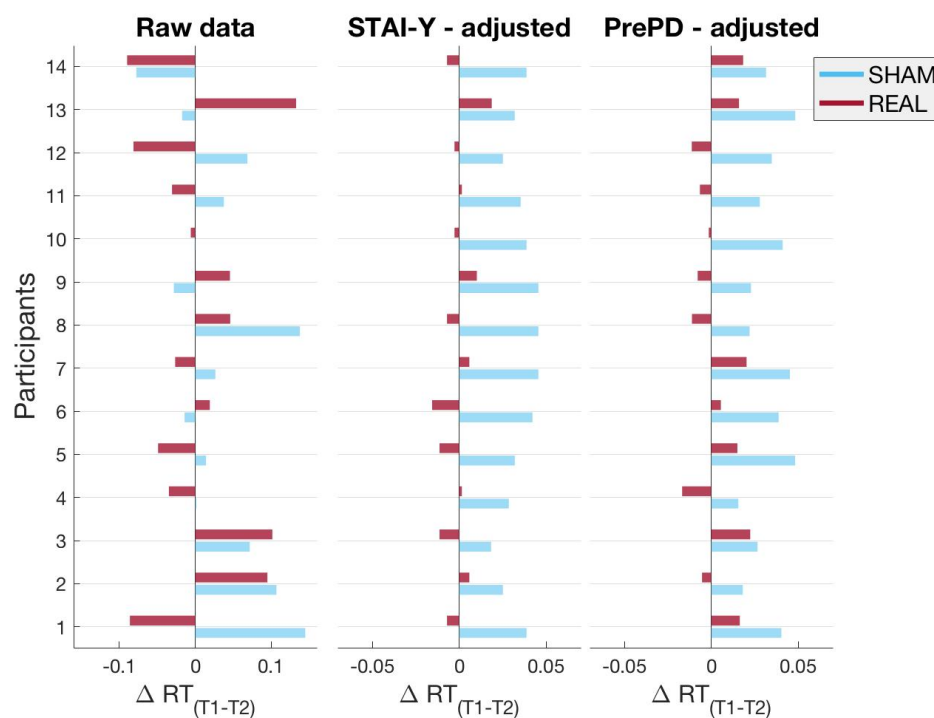


Fig. 4. Subject variability of reaction time change. Average log-based RT differences between the baseline (T1) and stimulation (T2) tasks are plotted on the vertical axis for each participant, separately for session sham (blue bars) and real (red bars). A different bar plot is used to represent mean differences from raw (left panel) and fitted data from the adjusted models using STAI-Y (middle panel) and PrePD (right panel) predictors. Negative and positive values on the horizontal axis indicate slower and faster performance, respectively.

3.2 Pupil dilation – PD

In the unadjusted LMM on PD, [AIC = 964.66], all fixed effects were significant [*Condition*: $F_{(1,1340)} = 10.46$, $p = .001$; *Time*: $F_{(1,1445)} = 15.83$, $p < .001$; *Trial*: $F_{(51,88)} = 5.94$, $p < .001$] except for the factor *Order* [$F_{(1,11)} = 1.96$, $p = .18$] and the interaction between *Condition* and *Time* [$F_{(1,1362)} = .75$, $p = .38$]. Importantly, pupil dilation decreased from T1 [$M = .375$; $SE = .023$] to T2 sessions [$M = .34$; $SE = .023$], indicating a general habituation of the phasic pupillary responses. However, no specific effect of tDCS on PD was revealed.

The adjustment for STAI-Y got worse the model fitting [AIC = 986.38], making the interaction *Condition x Time x STAI-Y* not significant [$F_{(1,1066)} = 1.08, p = .35$] (see Supplementary Table 2). On the contrary, adjusting for PrePD strongly improved the model fitting [AIC = -365.48], with significant PrePD [$F_{(1,1794)} = 2231.23, p < .001$] and interaction *Condition x Time x PrePD* effects [$F_{(3,1172)} = 6.5, p < .001$]. In detail, during the sham condition a decrease in pupil dilation consistently occurred throughout the range of PrePD values, whereas during real tDCS the pupil dilation progressively shifted toward a maximal suppression during trials with larger PrePD (Figure 5).

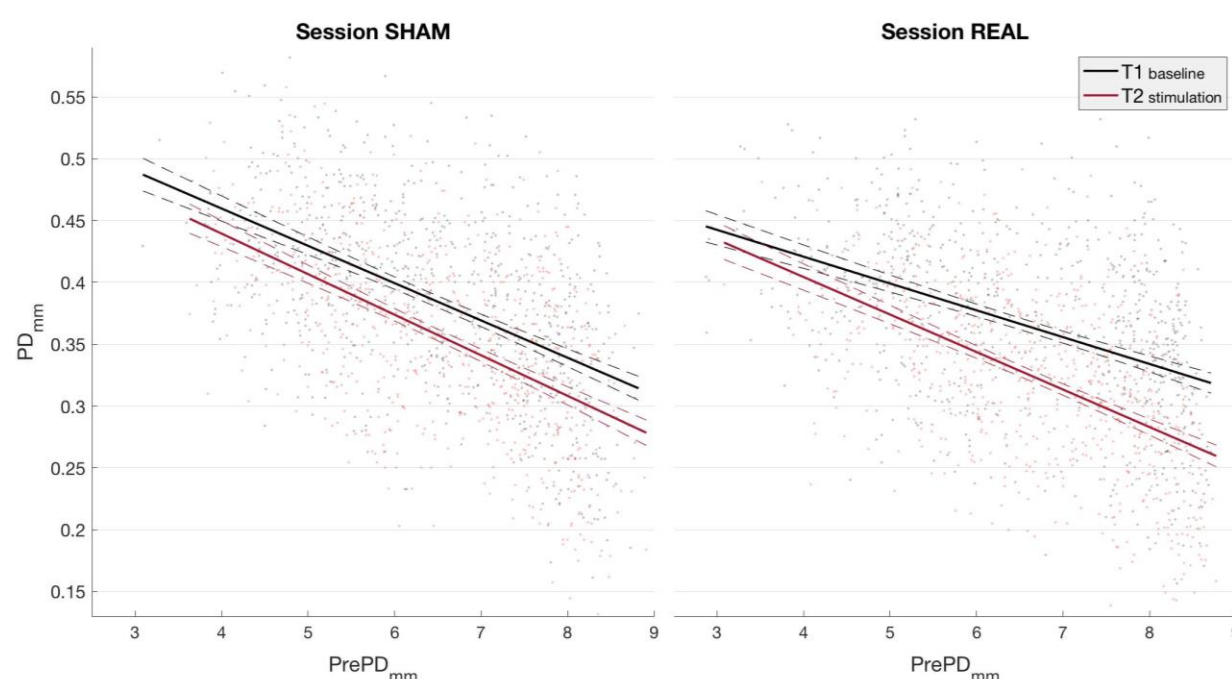


Fig. 5. Pupil dilations explained by physiological arousal. Model fitted PD values are plotted against pre-target pupil diameter, with results from session sham (left panel) and real (right panel). Grey and red best-fitting lines describe the trend of pupil dilation data points over pre-target pupil diameter respectively for the baseline (T1) and stimulation (T2) task. Dashed lines represent prediction functional bounds, i.e. the uncertainty of predicting the fitted lines.

4. Discussion

In the present study, we addressed the question of whether variable effects of single session tDCS could be dependent on the degree of arousal experienced before and during the experiment.

349 Subjective and physiological levels of arousal significantly accounted for the variation of reaction
350 times across two experimental sessions. Real tDCS appeared to hinder the practice effect observed
351 during the sham condition, with a trend becoming especially evident at higher levels of arousal. As
352 for pupil dilation, its values were significantly tied to the corresponding physiological fluctuations of
353 arousal. In particular, a more reduced pupillary response emerged during real tDCS as arousal levels
354 increased.

355 These results shed light on one relevant factor, which seems to account for the paucity of consistency
356 across tDCS effects in some experiments. What effectively emerges is that arousal is predictive of
357 the modulations induced by tDCS on task performance. A number of studies, which reported a
358 considerable inter- and intra-individual variability in response to tDCS protocols, investigated the
359 impact of demographic characteristics (e.g., age, gender), cortical architecture variations or
360 physiological measures specific to the targeted areas (e.g., levels of excitability of the primary motor
361 cortex), yet without considering general measures of activation comparable to arousal (9,64–68).

362 Here, we collected ratings on the subjective level of anxiety (i.e., STAI-Y State) before each
363 experimental session, thus serving as a fixed measure of arousal. Pre-target pupil diameter was instead
364 used as a dynamic proxy of arousal, allowing us to track its ongoing fluctuations (50,52,69). We
365 confirmed that pupil dilation values were negatively related with pre-target pupil diameter across all
366 conditions, as frequently reported in the literature (50,70–72).

367 When our measures of arousal were accounted for by statistical analyses, a clear picture emerged,
368 indicating that the effects induced by tDCS on the behavioral responses were dependent on both
369 subjective and physiological levels of arousal levels. In the sham session, participants speeded up
370 their responses when they completed the task for the second time. This practice effect emerged
371 somewhat independently of both the subjective and physiological levels of arousal, although a slightly
372 more pronounced improvement appeared with lower levels in either measures. During the application
373 of real tDCS, however, performance ceased to improve with the exception of trials characterized by
374 smaller pre-target pupil diameter and participants with a lower score at the STAI-Y questionnaire. A

negative or null behavioral outcome of anodal tDCS is not uncommon in the literature and learning impairments have been reported in a host of different tDCS studies involving specific learning outcomes, such as unimproved working memory for recognition or implicit categorization, blocked consolidation of visual perception and inhibited motor learning (68,73–78).

We chose response speed as behavioural measure, given that its intrinsic low sensitivity heavily relies on prior levels of fatigue and general activation (79–82). The interpretation of our behavioural results is arguably consistent with an inverted U-shape curve between task performance and arousal. According to this relationship, performance decline would occur when arousal levels are either too high or too low (33,83). None of the participants reported sleep deprivation or otherwise drowsiness-related conditions. Therefore, we can assume that the lower values of our predictors effectively corresponded to moderate and not low levels of arousal. With this in mind, the finding that facilitatory effects are principally associated with a moderate level of cortical excitation seems to support the proposed cellular mechanism for a cortical excitation-inhibition balance (16,84). On these grounds, tDCS exogenous modulation would negatively impact on the normal cortical functioning whenever the levels of endogenous neural activity increase to the extent of a dysfunctional neuronal gain, with spontaneous task disengagement causing slower responses. A direct consequence of this mechanism would be the inhibition of task learning effects, unless the endogenous system is sufficiently inactive, as in low arousal trials. The latter scenario provides an additional argument for when single session tDCS is found to improve task performance in the face of variable but otherwise moderate and well-balanced arousal levels. The understanding that an unbalanced combination of endogenous and exogenous excitability-increase events can, in fact, lead to negative effects is also coherent with frameworks on brain activity-dependent plasticity and on signal-to-noise ratio mechanisms (20,78). Results on pupil dilation, which represents a physiological response to relevant stimuli, corroborate the above interpretation. Only when the ongoing levels of arousal were considered in the analyses, a specific effect of tDCS on pupil dilatation was revealed. An overall reduction of pupil dilation occurred when participants completed the task for the second time (T2), consistently with a

physiological habituation effect that paralleled the practice effect seen in the behavioral results (85,86). In particular, pupil dilation evenly decreased for the entire range of arousal in the sham session, but crucial variations emerged during the application of real tDCS: looking at the lower end of the arousal range, pupil dilation values were not as much reduced as in sham session. Conversely, a more pronounced reduction in pupil dilation was observed in trials associated with higher arousal. These, in fact, corresponded to the trials of unimproved response times following real tDCS. Therefore, habituation of a phasic response may not necessarily indicate the same outcome direction as the better performance after a practice effect (85,87). Pupil dilations primarily reflect the timely increase of neural gain control, which translates into a system's responsivity amplification, and as such can be ascribed in the aforementioned inverted-U curve (34,50,71,88). The implication is that the additive effect of an exogenous neuromodulation would, on the one hand, contrast the natural habituation effect on pupil dilation occurring below the intermediate range of tonic arousal and, on the other hand, accentuate task disengagement at higher levels of tonic arousal, hence a greater reduction in phasic response. An analogous explanation was put forward in a recent tDCS work showing a reduction of pupil dilation - but no behavioral effects - during a Go-NoGo task, whereby it was argued that an offline tDCS enhancement of neuronal membrane potential could hinder or replace the endogenous gain control mechanisms of locus coeruleus (40).

Furthermore, outside the tDCS literature, phasic pupillary responses were found to be reduced whenever participants' attention was not directed to the task, such as during episodes of mind wandering (72,89–91). Indeed, recent empirical and theoretical formulations of mind wandering have proposed that the locus coeruleus–norepinephrine system is tightly linked to different internally-driven cognitive states, i.e., on- and off-task states with various degrees of deliberate control (36,92). In this respect, the possibility of a direct and focally targeted tDCS modulation of mind wandering has been recently debated with uncertain conclusions (93). Based on this knowledge, it is not unlikely that our tDCS effects would also be partly dependent on the arousal-mediated propensity of mind wandering activity during the task. Although not covered by the aims of this study, the above

possibility justifies the argument for a selective alteration of arousal via exogenous neuromodulation. For example, vigilance decrements and physiological sleep pressure were somewhat diminished after prolonged frontal anodal tDCS (41,94) with a magnitude of effects greater than caffeine (95,96). Whereas for the arousal modulation related to a specific event, stimulus-locked bursts of electric random noise stimulation were used to enhance performance and LC phasic responses, as indexed by skin conductance measurements (25). Despite this compelling evidence, it is still difficult to conclude that certain tDCS montages can directly modulate the deep brain arousal structures (97–99). Note though that other mechanisms could involve changes in the neocortical neurons, whose membrane potential shifts are known to be coupled with alteration in pupil diameter (34,100,101).

In summary, our data collectively offer an explanation for the negative or null effects of a common prefrontal tDCS application. We are aware that the interpretation of these particular results may not apply to all tDCS studies. Nevertheless, the large variability of arousal levels that we found across participants leads us to reflect more closely on what may mask the desired effects in the varied and still growing landscape of stimulation studies, which often fail to incorporate, but simply acknowledge, the crucial aspect of individual state-dependent variables (102–105).

The importance of brain state is not a novel idea in the literature on non-invasive brain stimulation. The ongoing or basal levels of activation, included in the concept of “state-dependency”, have been extensively reported to impact the effects of transcranial magnetic stimulation (TMS) (106). Nevertheless, considering the mechanisms of action of tDCS, which modulates excitability of neurons by hyperpolarizing or depolarizing their membrane potential (107,108), tDCS effects might be more sensitive to the arousal levels than TMS. In a similar vein, these considerations might be applicable to any kind of current stimulation modality.

Taken together, the discussed findings should encourage a more careful interpretation of null or negative effects of tDCS. This is far from saying that all replication failures are due to inherently

inefficacious tDCS protocols with exhausted future potential (15). Such observations should instead help ascribing the outcome of those protocols to the interrelation of the locus coeruleus–norepinephrine system and the spreading of induced currents in the brain (40,42). In this sense, future tDCS studies might consider useful to have both dynamic and fixed measures of arousal as an accurate way to monitor its impact on the final outcome. If successful, these achievements would be of great help also in assessing the degree of effectiveness with which tDCS protocols are being utilized to treat or ameliorate clinical conditions.

Disclosure statement

This work has not been published and has not been submitted for publication elsewhere while under consideration. The authors declare no potential conflict of interest.

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